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May 29, 2018

Paulette M. Gaynor,
Office of Food and Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5001 Campus Drive
College Park, MD 20740

re: GRAS Notification for the Use of Calcium Propionate on Processed (Sliced/Cut) Fruits and Vegetables

Dear Dr. Gaynor:

Pursuant to 21 CFR Part 170, Wonderful Citrus, LLC, hereby provides notice of a claim that the food ingredient described in the enclosed notification document is exempt from the premarket approval requirement of the Federal, Food and Drug and Cosmetic Act because it has been determined to be generally recognized as safe (GRAS), based on scientific procedures, for use on processed fruits and vegetables.

As specified in 21CFR §170.210, we are providing a copy of the notification on the enclosed CD-ROM. If you have any questions about this submission or require additional information, please contact me at (202) 393-3903, ext. 114 or eharrison@lewisharrison.com

Sincerely,

(b) (6)

Eliot Harrison,
Agent for Wonderful Citrus, LLC

Generally Recognized as Safe (GRAS) Notice for the Use of Calcium Propionate as an Antibrowning Agent in Processed Fruits and Vegetables

Submitted on Behalf of Wonderful Citrus, LLC

Prepared by:
Lewis & Harrison, LLC
122 C Street, NW
Suite 505
Washington, DC 20001
Tel: 202-393-3903

May 29, 2018

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Part 1. Signed Statements and Certification

Pursuant to 21 CFR, Part 170, subpart E, Wonderful Citrus, LLC ("Wonderful") is submitting this Generally Recognized as Safe ("GRAS") Notice for the use of calcium propionate as an antibrowning agent on processed (e.g., cut/sliced) fruits and vegetables. As described in Parts 2 through 7 of this GRAS Notice, Wonderful is claiming that calcium propionate is not subject to the premarket approval requirements of the Federal Food, Drug and Cosmetic Act ("FFDCA") based on its conclusion that calcium propionate is GRAS under the proposed conditions of use.

1.1 Name and Address of Notifier

Contact Person: Dr. Ram Uckoo
Company Name: Wonderful Citrus, LLC
Address: Delano, 1901 S. Lexington Street, Delano, CA 93215
Telephone Number: (661) 720-2400
E-mail Address: ram.uckoo@wonderful.com

1.2 Common Name of Notified Substance

The common name for the notified substance is calcium propionate. It is a component in an aqueous formulation that also contains calcium ascorbate and calcium chloride. As applied to processed fruits and vegetables, the formulation contains approximately 5% calcium ascorbate, 1% calcium propionate and 0.2% calcium chloride. The remaining constituent is water.

1.3 Conditions of Use of the Notified Substance

Calcium propionate will be part of a formulation that is used to treat processed fruits and vegetables in order to control enzymatic browning in these foods. The application procedure for calcium propionate involves dipping, spraying, or immersing fruits and vegetables into a container holding the aqueous formulation of calcium chloride, calcium ascorbate and calcium propionate. Any remaining liquid on the treated fruits and vegetables is then removed by centrifuging or similar removal processes.

1.4 Purpose for Which the Substance is Used

The combination of calcium propionate, calcium chloride and calcium ascorbate is highly effective in inhibiting enzymatic browning in processed fruits and vegetables. Enzymatic browning primarily affects the aesthetic quality of fruits and vegetables and, to a lesser extent, can also adversely affect their flavor and nutritional value.

1.5 Description of the Population Expected to Consume the Substance

Since calcium propionate will be used to treat fruits and vegetables, without geographical or other restrictions, dietary exposure will occur throughout the general population.

1.6 Basis for GRAS Determination

The basis for the GRAS determination regarding the use of calcium propionate as an antibrowning agent in processed fruits and vegetables is scientific procedures.

1.7 Availability of Information

The data and information that serve as the basis for this GRAS determination will be sent to the FDA upon request, or are available for FDA's review and copying at reasonable times at the office of Lewis & Harrison, LLC, at the following address:

122 C Street, N.W.
Suite 505
Washington, D.C. 20001

In addition, should the FDA have any questions or additional information requests concerning this notification during or after the Agency's review of the notice, Lewis & Harrison will supply these data and information as requested.

1.8 Freedom of Information Act, 5 U.S.C. Section 552

None of the data presented in parts 2 through 7 of this notice contain any trade secret, commercial, or financial information that is privileged or confidential; therefore, all data and information presented herein are not exempt from the Freedom of Information Act, 5 U.S.C. Section 552.

1.9 Certification

We certify that, to the best of our knowledge, our GRAS notice is complete, representative, and a balanced submission that includes unfavorable information, as well as favorable information, available and pertinent to the evaluation of the safety and GRAS status of the use of calcium propionate as an antibrowning agent for processed fruits and vegetables.

(b) (6)

(Eliot Harrison for Ram Uckoo)

Name: Ram Uckoo, Ph.D.
Title: Research and Development Manager

5/29/2018
Date

Part 2. The Identity, Method of Manufacture, Specifications and Physical and Technical Effect of the Notified Substance

Chemical and regulatory information regarding calcium propionate is presented below.

2.1 Identity

Common or Usual Name: Calcium propionate

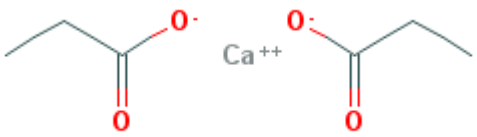
Chemical Name: Calcium propionate

Chemical Abstracts Service (CAS) Number: 4075-81-4

Empirical Formula and Formula Weight: $C_6H_{10}O_4Ca$

Chemical Structure:

Figure: Calcium propionate[1]



Current Regulated Food Uses:

Calcium propionate is affirmed as Generally Recognized as Safe (GRAS), under 21 CFR §184.1121, when used as an antimicrobial agent, at a level not to exceed good manufacturing practice, in the following foods: baked goods, cheeses, confections and frostings, gelatins, puddings and fillings.

2.2 Manufacturing Information and Specifications

The notifier will purchase calcium propionate from suppliers that meet the manufacturing requirements in 21 CFR §184.1121 for calcium propionate or the alternative manufacturing process described in GRAS Notice No. 157. Specifically, calcium propionate is prepared by neutralizing propionic acid with calcium hydroxide or by hydrolyzing propionitrile with calcium hydroxide and then removing ammonia.

[1] https://pubchem.ncbi.nlm.nih.gov/compound/calcium_propionate#section=Names-and-Identifiers

The specifications for calcium propionate will meet the provisions established in the most recent Food Chemicals Codex (FCC) for this substance. Specifically, the assay for food-grade calcium propionate requires that the substance contains not less than 98.0% and not more than 100.5% of calcium propionate on the anhydrous basis. In addition, the level of metals (as Pb) cannot exceed 10 mg/kg; the fluoride level cannot exceed 0.003%, insoluble substances cannot exceed 0.2%, and water cannot exceed 5.0%.

As noted above, calcium propionate is a component of an antibrowing formulation that also contains calcium ascorbate and calcium chloride. For a 500-gallon batch of the formulation, the following amounts of each substance will be added:

- 94.63 kg (calcium ascorbate)
- 18.92 kg (calcium propionate)
- 3.785 kg (calcium chloride)

The batch is then made up to volume with potable water. The manufacturing process is a simple mixing procedure. No purification procedures or processing aids are used during the process.

2.3 Intended Technical Effect

In several efficacy trials, it has been demonstrated that the antibrowning formulation containing calcium propionate significantly inhibits enzymatic browning in processed fruits and vegetables. The antibrowning activity was effective for up to three weeks when compared to untreated controls.

Part 3. Dietary Exposure

3.1 Dietary Exposure from the Proposed Use

Dietary exposure to calcium propionate can result from the consumption of processed fruits and vegetables that are treated with the antibrowning formulation containing calcium propionate. Since calcium propionate readily dissociates when diluted in water, dietary exposure will occur to calcium and propionate ions.

In a residue study conducted at California Polytechnic State University, residue levels of ascorbate, propionate and chloride were measured after treatment of pre-cut apples. The apples were submerged in the formulation containing these components (5% calcium ascorbate, 1% calcium propionate and 0.2% calcium chloride and then centrifuged and dried. The results are shown in Table 1 below.

Table 1
Average Residue Levels of Ascorbate, Propionate and Chloride
After Treatment with Antibrowning Formulation

Ingredient	Residue Level (mg/kg apple)
Ascorbate	736.18 Standard Deviation: 137.22
Propionate	147.22 Standard Deviation: 27.44
Chloride	29.44 Standard Deviation: 5.49

Although the residue levels of calcium were not assayed, the calcium level can be calculated by assuming that calcium and propionate ions are similarly retained on treated apples. Based on this assumption, the calcium residue is then derived by multiplying the percent calcium in calcium propionate by the residue level of chloride.

Calcium Residue = Propionate Residue on Fruit (147.22 mg/kg fruit) × Percent Calcium in Calcium Propionate (21.0%)

Calcium Residue = 30.9 mg/kg fruit

The estimated daily intake (EDI) of calcium and propionate can then be quantified by multiplying the anticipated residue levels of calcium and propionate in treated fruits and vegetables by the dietary consumption of these food commodities.

The notifier expects that the antibrowning formulation will be used predominantly on processed apples and lemons and that almost all dietary exposure to calcium and propionate are expected to result from use on these foods. The estimated daily intake (EDI) for apples and lemons can be derived from the *Food Commodity Intake Database (FCID) Consumption Calculator*, which uses the National Health and Nutrition Examination Survey/What We Eat in America (NHANES/WWEIA) food intake and recipe data to estimate food commodity consumption (http://fcid.foodrisk.org).

The daily intakes of apples and lemons for both young children and adults are shown in Table 2 below. For the child and adult exposures, body weights of 10 kg and 80 kg, respectively, were used. Dietary intakes are calculated on both an mg/kg and g/day basis.

Table 2
Daily Intake Values for Apples and Lemons

Population Group	Apple, fruit with peel/Apple Peeled Fruit	Lemon, /Lemon Juice/Lemon Peel
Child (10 kg)	4.8 g/kg/day (90th percentile)*, or 48 g/day for an 10 kg child	0.3 g/kg/day (90th percentile) ** or 3 g/day for an 10 kg child
Adult (80 kg)	1.4 g/kg/day (90th percentile)*, or 112 g/day for an 80 kg adult	0.1 g/kg/day (90th percentile)**, or 8 g/day for an 80 kg adult

*Results from FCID Consumption Calculator, page 10 of this notice
**Results from FCID Consumption Calculator, page11 of this notice

FCID Consumption Calculator Reports [Per Capita, Two-Day Average Consumption Commodity Mass (g) per Body Mass (kg) per Day (d)]

			N	Percent Consuming	Mean	SE	1%	5%	10%	15%	20%	25%	30%	35%	40%	45%	50%	55%	60%	65%	70%	75%	80%	85%	90%	95%	97.5%	99%	Max
Apple, fruit with peel | Apple, peeled fruit																													
Age Range	**Gender**	**Race**																											
All ages	All	All	24,673	24	0.37	0.02	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.3	0.8	1.3	2.1	3.1	4.8	26.9†
Birth to < 12 months	All	All	1,190	7	0.22	0.06	0†	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.7	2.3	8.6†	17.3†
1 to < 3 years	All	All	1,479	34	1.37	0.11	0†	0	0	0	0	0	0	0	0	0	0	0	0	0	0.7	1.6	2.5	3.8	4.8	7.5	10.1	12.5†	26.9†
3 to < 6 years	All	All	1,418	31	1.18	0.12	0†	0	0	0	0	0	0	0	0	0	0	0	0	0	<0.05	1.3	2.3	3.3	4.5	6.0	8.4	11.4†	24.3†
6 to < 13 years	All	All	3,316	28	0.65	0.04	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.4	1.2	1.8	2.5	3.7	4.8	7.0	22.8†
13 to < 20 years	All	All	3,486	21	0.32	0.03	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	<0.05	1.0	1.4	1.9	2.7	3.7	7.4†
20 to < 50 years	All	All	6,974	20	0.23	0.01	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	<0.05	0.4	1.0	1.5	2.2	2.9	14.1†
50 years and older	All	All	6,810	27	0.28	0.02	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.1	0.4	0.8	1.1	1.7	2.2	3.0	9.4†
13 to < 50 years	Female	All	5,543	20	0.25	0.02	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	<0.05	0.4	1.1	1.7	2.3	3.1	9.0†

Notes: '†' indicates estimates are less statistically reliable based on np < 8 * 'Design Effect' guidance published in the Joint Policy on Variance Estimation and Statistical Reporting Standards on NHANES III and CSFII
The **"Two-day average"** results are based on the average of the two days of food consumption reported in the NHANES/WWEIA survey for those "both day" respondents. If the respondent reports zero consumption on one of the two days and non-zero consumption on the other day, his/her average consumption would be the average of zero and nonzero consumption. Calculation performed on 12/6/2017 using FCID-WWEIA data for years 2005-2010 from http://fcid.foodrisk.org/percentiles

Lemon | Lemon, juice | Lemon, peel																											
Age Range	**Gender**	**Race**																									
All ages	All	All	24,673	66	0.05	<0.005	0	0	0	0	0	0	0	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	0.1	0.1	0.3	0.5	0.9	7.2†
Birth to < 12 months	All	All	1,190	8	0.03	0.02	0†	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	<0.05	0.1	0.5†	6.0†
1 to < 3 years	All	All	1,479	53	0.11	0.01	0†	0	0	0	0	0	0	0	0	0	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	0.1	0.2	0.3	0.6	0.9	1.9†	4.3†
3 to < 6 years	All	All	1,418	66	0.12	0.01	0†	0	0	0	0	0	0	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	0.1	0.1	0.2	0.3	0.7	1.0	1.4†	5.5†
6 to < 13 years	All	All	3,316	65	0.09	0.01	0	0	0	0	0	0	0	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	0.1	0.1	0.2	0.5	0.8	1.4	7.2†
13 to < 20 years	All	All	3,486	62	0.05	<0.005	0	0	0	0	0	0	0	0	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	0.1	0.2	0.5	0.9	5.3†
20 to < 50 years	All	All	6,974	68	0.05	<0.005	0	0	0	0	0	0	0	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	0.1	0.3	0.5	0.7	5.9†
50 years and older	All	All	6,810	68	0.03	<0.005	0	0	0	0	0	0	0	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	0.1	0.1	0.3	0.6	2.9†
13 to < 50 years	Female	All	5,543	68	0.05	<0.005	0	0	0	0	0	0	0	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	0.1	0.1	0.3	0.5	0.8	2.7†

Notes: '†' indicates estimates are less statistically reliable based on np < 8 * 'Design Effect' guidance published in the Joint Policy on Variance Estimation and Statistical Reporting Standards on NHANES III and CSFII
The "**Two-day average**" results are based on the average of the two days of food consumption reported in the NHANES/WWEIA survey for those "both day" respondents. If the respondent reports zero consumption on one of the two days and non-zero consumption on the other day, his/her average consumption would be the average of zero and nonzero consumption. Calculation performed on 12/6/2017 using FCID-WWEIA data for years 2005-2010 from http://fcid.foodrisk.org/percentiles

Based on the residue levels for propionate and calcium (page 8 of this Notice) and the daily intakes for apples and lemons, the EDI for propionate and calcium from the use of the antibrowning formulation is shown below. It is assumed that the residue levels in lemons for propionate and calcium will be the same as those measured and calculated for apples.

Propionate

Child

- Apples:

  (48 g/day) (0.147 g/1000 g of apples) = 7×10^{-3} g/day or 7.0 mg/day

- Lemons

  (3 g/day) (0.147g/1000 g of lemons) = 4×10^{-4} g/day or 0.4 mg/day

Accordingly, the total intake of propionate for children, at the 90th percentile, is 7.4 mg/day.

Adults

- Apples:

  (112 g/day) (0.147 g/1000 g of apples) = 1.6×10^{-2} g/day or 16.4 mg/day

- Lemons

  (8 g/day) (0.147 g/1000 g of lemons) = 1.1×10^{-3} g/day or 1.1 mg/day

Accordingly, the total intake of propionate for an adult, at the 90th percentile, is 17.5 mg/day.

Calcium

Child

- Apples:

  (48 g/day) (0.03 g/1000 g of apples) = 1.4×10^{-3} g/day or 1.4 mg/day

- Lemons

  (3 g/day) (0.03 g/1000 g of lemons) = 9×10^{-5} g/day or 0.09 mg/day

Accordingly, the total intake of calcium for children, at the 90th percentile, is 1.5 mg/day.

Adults

- Apples:

  (112 g/day) (0.03 g/1000 g of apples) = 3.3 x 10^{-3} g/day or 3.3 mg/day

- Lemons

  (8 g/day) (0.03 g/1000 g of lemons) = 2.4 x 10^{-4} g/day or 0.24 mg/day

Accordingly, the total intake of calcium for adults, at the 90th percentile, is 3.5 mg/day.

3.2 Dietary Exposure from Existing Uses

Dietary intake values for calcium and propionate have been reported in previously submitted GRAS Notices and are summarized below.

Propionate

The daily intake of calcium propionate was calculated in GRAS Notice No. 157, (https://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm264105.pdf). According to this notice, the average daily intake of calcium propionate is 220 mg/person/day (page 15 of the GRAS Notice), which is equivalent to 180 mg/person/day of propionate. The EDI for propionate, from the use of calcium propionate as an antibrowning agent for processed fruits and vegetables, at the 90th percentile, is 7.4 mg/day (child) and 17.5 mg/day (adult). Consequently, the EDI for propionate, resulting from the antibrowning use, will be less than 10% of the average daily intake of propionate from all food uses.

Calcium

The dietary intake of calcium was presented in GRAS Notice No. 634, https://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm505252.pdf. The notice reported that for the U.S. population, age 1 year and older, the *per user* intake of calcium at the 90th percentile is 1,936 mg/day (see page 26 of the Notice). The EDI for of calcium, from the use of calcium propionate as an antibrowning agent for processed fruits and vegetables, at the 90th percentile, is 1.5 mg/day (child) and 3.5 mg/day (adult). Consequently, the antibrowning use results in a daily intake that is approximately 0.2% of the total daily intake of calcium at the 90th percentile.

Part 4. Self-Limiting Levels of Use

Calcium propionate will only be added to processed fruits and vegetables at levels to achieve its technological function. The notifier is unaware of any self-limiting levels of use associated with calcium propionate.

Part 5. Experience Based on Common Use in Food Before 1958

Although calcium propionate has a long history in food prior to 1958, the notifier is unaware if this ingredient has ever been used as an antibrowning agent in processed fruits and vegetables, including prior to 1958.

Part 6. Safety Evaluation and Basis for Our Conclusion of GRAS Status

As noted above, calcium propionate will dissociate into calcium and propionate ions. Accordingly, the safety assessment focuses on both of these ions as well as calcium propionate.

Calcium

The Health and Medicine Division (HMD, formerly the Institute of Medicine) of the National Academy of Sciences established an Upper Limit (UL) for calcium of 2,500 mg/person/ day from all sources (e.g., food and supplements) for all age groups, including pregnant or lactating women, based on the risk for hypercalcemia and renal insufficiency at intakes ranging from 4,000 to 5,000 mg of calcium/person/day and greater (IOM, 1997)[2]. A UL for infants aged 0 to 12 months could not be established due to insufficient data. The IOM was subsequently asked to review the current data and in 2011 published updated ULs (IOM, 2011)[3].

For infants, new data were available regarding calcium excretion that suggested that infants can tolerate intakes of up to approximately 1,750 mg/day. Thus, a no-observed-adverse-effect level (NOAEL) of 1,750 mg/day was established. For infants 0 to 6 months of age, an uncertainty factor of 2 was applied to account for body weight differences and the UL was set at 1,000 mg/day. The UL for infants aged 7 to 12 months was set at 1,500 mg/day since an increased capacity to handle calcium will accompany increased body size.

The UL for children aged 1 through 8 was not changed and remains at 2,500 mg/day, whereas the UL for children aged 9 to 13 years and adolescents aged 14 to 18 years, including pregnant and lactating adolescents, was raised by 500 mg/day to 3,000 mg/day to account for the increase in bone accretion and likely accompanying increases in tolerated intakes. For adults, although the IOM recognized that hypercalcemia was an adverse outcome, they noted that it was a disease state and they did not consider it appropriate for the derivation of ULs for the normal, healthy population. Kidney stone formation was selected as the indicator, and an UL of 2,000 mg/day was set for adults aged 51 to 70 and greater than 70 years based on increased risk of kidney stone formation at higher intakes.

[2] IOM (1997). Calcium. In: *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride.* Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine (I0M). Washington (DC): National Academy Press (NAP), pp. 71-145. Available from: http://books.nap.edu/openbook.php?isbn=0309063507&paqe=71.

[3] IOM (2011). *Dietary Reference Intakes for Calcium and Vitamin D.* Washington (DC): National Academy of Science (NAS), Institute of Medicine (I0M), Food and Nutrition Board. Available at: http://www.nap.edu/cataloq.php?record id=13050.

It was noted by the IOM committee that "intakes of calcium from food do not readily result in excess intakes and are not associated with adverse effects; rather, the adverse effects appear to be a function of calcium supplementation added to baseline intake" (IOM, 2011)[3]. Although kidney stone formation does occur in younger adults, the IOM committee noted that it does not appear to be correlated with calcium supplement use, and thus established an UL of 2,500 mg/day for adults, including pregnant and lactating women, aged 19 to 30 and 31 to 50 years using an interpolation approach based on the mid-point between the UL for adolescents and persons greater than 50 years of age.

The European Commission's Scientific Committee on Food (SCF) established a UL of 2,500 mg/person/day from all sources for all age groups, including pregnant or lactating women, based on no adverse effects observed at this intake level in human studies (SCF, 2003)[4].

Calcium Propionate

Overview

Toxicological studies have been conducted with propionic acid, sodium propionate, calcium propionate and calcium dipropionate. All of these substances should be considered toxicogically equivalent; therefore, the data on propionic acid, sodium propionate and calcium dipropionate can be bridged to calcium propionate.

Propionic acid, sodium propionate, and calcium propionate have demonstrated low acute toxicity after oral administration to mice or rats. Several assays for mutagenicity of propionic acid and calcium and sodium propionate were negative. Investigations of the teratogenicity of calcium propionate in were negative. Long-term feeding studies of propionic acid and calcium propionate have not been reported. However, a long-term feeding study conducted with sodium propionate showed no adverse effects in rats and, as noted above, sodium propionate can be considered toxicologically equivalent to calcium propionate.

[4] SCF (2003). *Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Calcium* (expressed 4 April 2003). (SCF/CS/NUT/UPPLEV/64 Final). European Commission, Scientific Committee on Food (SCF). Available at:https://ec.europa.eu/food/sites/food/files/safety/docs/sci-com_scf_out194_en.pdf

Based on the above, an expert committe (SCOGS) concluded that there is no evidence in the available information on propionic acid, calcium propionate, and sodium propionate that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that are now current or that might reasonably be expected in the future[5].

Toxicity Studies

- **Acute Toxicity**

The oral LD_{50} in rats for calcium propionate ranged from 2600 to >5000 mg/kg. The 4 hr. acute inhalation LC_{50} in rats is >5.0 mg/L and the acute dermal LD_{50} in rabbits is 500 mg/kg. Calcium dipropionate is reported to be non-irritating to either the eyes or the skin[6].

- **Genotoxicity**

In the bacterial mutation assay (Ames Test), calcium dipropionate was evaluated in the following *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538, with and without S9 metabolic enzymes. Under the conditions of the assay, calcium dipropionate and was found to be non-mutagenic (IUCLID, 2000)[7].

In a bacterial point mutation assay, sodium and calcium propionate were assayed for gene mutation with six *Salmonella typhimurium* strains (TA92, TA94, TA98, TA100, TA1535 and TA1537), in the absence or presence of a rat liver metabolic activation system.
The maximum concentrations of sodium and calcium propionate studied were 5 and 10 mg/mL, respectively. Both chemicals tested negative in the assay (IUCLID, 2000)[7].

In a separate bacterial point mutation assay, calcium propionate was assayed for gene mutation with *S. typhimurium* strains (TA1535, TA1537 and TA1538) and for gene conversion with *Saccharomyces cerevisiae* strain D4 in the absence or presence of exogenous mouse, rat and monkey liver metabolic activation systems.
Negative results were obtained, but it is noted that the study had poorly reported concentration levels and experimental designs (EFSA, 2014[8]).

[5] Calcium Propionate; Dilaurryl thiodipropionate; Propionic acid; Sodium propionate; Thiodipropionic acid. SCOGS Report No.: 79, NTIS Accession No.: PB80104599, 1979.
[6] OM Group, Inc. Summary of Existing Data, Proposed Test Plan and Rationale for Calcium Dipropionate (CAS# 4075-81-4). US EPA High Production Volume (HPV) Chemical Challenge Program. April 24, 2007.
[7] IUCLID Dataset (2000). Calcium Dipropionate CAS# 4075-81-4. European Commission – European Chemicals Bureau, 18-February 2000.
[8] EFSA (2014). Scientific Opinion on the Re-Evaluation of Propionic Acid (E280), Sodium Propionate (E281), Calcium Propionate (E282) and Potassium Propionate (E283) as Food Additives. EFSA Panel on Food Additives and Nutrient Sources Added to Food (ANS). EFSA Journal 12(7); 3779, 2014.

In a separate study, calcium propionate was tested for mutagenicity in *S. typhimurium* strains G-46 and TA1530 and for recombinogenic properties in *S. cerevisiae* strain D3. Negative findings were reported, but it is noted that the study had poorly reported concentration levels and experimental design (EFSA, 2014)[8].

Calcium propionate was also non-mutagenic when tested in the *in vitro* Chinese Hamster Lung Cell (CHL, V79 cells) Test, with and without metabolic activation (S9) (EFSA, 2014)[8].

Calcium dipropionate was negative in the cytogenetic and dominant lethal assays. Propionic acid was negative in a micronucleus test. In the *in vivo* mouse micronucleus assay studies, calcium dipropionate showed no chromosomal aberrations in rat bone marrow cells and no dominant lethal mutations were observed[9].

In a bone marrow chromosomal aberration assay, rats were administered 0, 50, 500 or 5000 mg/kg bw of calcium propionate by oral gavage as a single dose (59 animals) or daily for five consecutive days (18 animals). The animals were euthanized six, 24 or 48 hours after dosing in the single treatment groups and six hours after the last dose in the repeated treatment groups. Chromosomal aberration and mitotic index were determined in this study and calcium propionate did not induce statistically significant increases at any treatment level[7,8].

In a rat bone marrow cytogenetic assay, sodium propionate was tested for genotoxicity effects and negative findings were reported. No further details were provided for the study[7, 8].

In a host-mediated assay, male mice were administered 50, 500 or 5000 mg/kg bw of calcium propionate by oral gavage as a single dose or daily for five consecutive days. Positive and negative control groups were included in both single and repeated treatments. The *S. typhimurium* strains (G-46 and TA1530) and *S. cerevisiae* strain D3 were used as indicator organisms for inducing reverse mutation and mitotic recombination, respectively. In the single dose treatment, all animals received 2 mL of the indicator organisms (3 ×

[9] Litton Bionetics, 1974a. Summary of mutagenicity screening studies host-mediated assay cytogenetics dominant lethal assay contract FDA 71-268, compound FDA 71-36, calcium propionate. LBI Project 2446. March 1973, revised September 1974. Cited in EFSA Journal 12(7):3779, 2014

10^8 cells for *S. typhimurium* and 5×10^8 cells for *S. cerevisiae*) immediately after treatment by intraperitoneal (i.p.) injection. The animals were euthanized three hours later with the indicator organisms removed from the peritoneal cavity and plated for colony scoring. Results indicated a non-dose-related increase in the reversion frequency of *S. typhimurium* strain G-46. Therefore, the results were considered not biologically relevant. Negative findings were reported for strains TA1530 and D3[7 8].

In a dominant lethal assay, male rats were administered 50, 500 or 5000 mg/kg bw of calcium propionate by oral gavage as a single dose, or daily for five consecutive days. Positive and negative control groups were included in both single and repeated treatments. Following treatments, the animals were sequentially mated with two untreated virgin females, five days/week for eight weeks. At the end of the treatment every week, the females were replaced with two untreated virgin females. The treated females were removed from the males, housed separately and euthanized 14 days after separation. The uteri were analyzed for early and late fetal deaths and total implantations. Negative findings were reported in the study[7, 8, 10].

- **Short-term/Subchronic Studies**

Repeat dose studies with calcium dipropionate, sodium propionate and propionic acid were conducted in rats and dogs, with study periods ranging from 4 weeks to 90 days with exposure levels ranging up to 3320 mg/kg/day. No abnormalities in clinical or hematological examinations were observed. Changes in the forestomach (e.g., hyperkeratosis and hyperplasia) were observed. These changes were observed to occur equally with calcium and sodium propionate, but were more marked with exposure to propionic acid. The changes were largely reversible, attributed to the acidity of the compound, and were not related to any systemic toxicity of the compound. The no-observable effect-level was considered to be 3320 mg/kg/day[11].

In a repeat dose toxicity study, rats were fed 0, 830 or 2490 mg/kg bw/day of sodium or calcium propionate in their diet for 3–4 weeks. The only endpoint measured in this study was growth and no effect was observed[7].

[10] US EPA TSCA (2007) Summary of Existing Data, Proposed Test Plan and Rationale for Calcium Dipropionate (CAS# 4075-81-4). US EPA High Production Volume (HPV) Chemical Challenge Program 201-16574B. April 24, 2007.

[11] Altman H-J and Grunow, W. 1988a. Ergeb. Neuer. Fuetterungsvers. m.Propions.u.i.Salzen“ unpubl. Report Fed. Health Agency (BGA Berlin,’88). As cited in IUCLID (2000); Altman H-J. and Grunow, W., 1988b. Arbietspapier zur Tox. V. Propions. U.i. Ca-, K-, und Na-Saltze, unpubl. Report Fed Health Agency, BGA Berlin,88; and Harshbarger, K.E., 1942. Report of a study on the toxicity of several food preserving agents. J. Dairy Sci. 25:169-174. Also cited and interpreted in FASEB (1979). Were all cited in US EPA HPV Program document, April 24, 2007.

Groups of 40 female Wistar rats were fed 0 or 1320 mg/kg bw/day of sodium propionate in their diet for a year. No changes were observed in the blood, clinical chemistry or urine tests. No changes in organ weights were observed in the study. The average body weight at the end of the study was 290 g in treated animals compared with 299 g in control animals, but the slight reduction in growth rate was not considered to be significant[7,11].

Wistar rats were maintained on a normal diet, or diet consisting of 75% bread that was baked with the addition of a 50-fold amount of four bread additives and bleached flour for a year. bSodium propionate at a concentration of 5 % was one of the additives. Although it would not be possible to determine the attribution of effects given the complex mixture of substances in this study, no clinical or pathological effects were observed. Therefore, the chemical was concluded to not cause toxic effects[7].

In a separate study, Wistar rats (five animals/sex/group) were fed 0 or 40000 ppm (approximately 3320 mg/kg bw/day) of calcium propionate in their diet for four (females) and eight (males) weeks. Following four weeks of oral exposure to the chemical, the treated animals showed slightly thickened limiting ridge in the forestomach and more pronounced hyperkeratosis and hyperplasia of mucosa. More pronounced lesions were observed in the forestomach after eight weeks of exposure. The effects were reversed following an eight-week treatment-free period[7].

In a repeated dose toxicity study in beagle dogs, calcium propionate at concentrations of 0, 14500 or 43500 ppm in the diet was fed to the animals for 90 days. Diarrhea and vomiting were observed in all animals at the highest concentration and one animal in the 14500 ppm group. (NOAEL 14500 ppm approximately equal to 260 mg/kg bw) Spontaneous epithelial hyperplasia of the esophageal mucosa was observed in all groups and was concluded to be not related to treatment. No further details were provided[7].

In a repeated dose toxicity study in 12 monkeys, sodium propionate was fed at a concentration of 2 % (equivalent to 420 mg/kg bw/day) in the diet for nine weeks. Hematological and liver effects were studied and no toxic effects were observed[7].

- **Long-term Toxicity Studies**

In a chronic study conducted with Charles River CD rats (40 sex/group), the test animals were fed 2.05% of sodium propionate in the diet (equivalent to 1025 mg/kg-bw/day) for 104 weeks. No adverse effects on bodyweight gain, food consumption, hematology, blood chemistry, organ weights or mortality was observed when compared to control rats receiving a basal diet. There was an increased incidence and earlier onset of spontaneous subepithelial basophilic deposits in the renal pelvis among treated rats. No other histological findings of significance were mentioned. The organs evaluated by histopathology were not mentioned in detail (EFSA, 2014)[8].

In a lifetime study conducted with an analogue chemical, propanoic acid, male Wistar rats (30 animals/group) were administered this substance in their diet at doses of 0, 264 or 2640 mg/kg-bw/day for 20 weeks or for their lifetime. Ten animals from each group were euthanized at week 20 and the remaining animals were fed with their respective diets until death. No treatment-related effects were observed in the animals treated at 264 mg/kg-bw/day. In the animals treated at 2640 mg/kg-bw/day, forestomach epithelial changes such as hyperplasia and hyperkeratosis were observed at week 20. The other permanent effects included hyperplasia with ulceration, dyskeratosis and papillomatous elevations. One animal euthanized two years after treatment had hyperplasia with ulceration and unspecified 'carcinomatous changes' along with erosive changes in the glandular region of the stomach[12]. It was concluded that the effects observed were due to chronic irritation and inflammation and the associated hyperplastic proliferative repair response. Only forestomach lesions related to chronic irritation were reported. Humans lack this organ and there is no correlation between the forestomach in rats and esophageal lesions in humans.

It should be noted that the EFSA Panel that evaluated propionic acid and the propionates (sodium propionate, calcium propionate and potassium propionate) indicated that, for these substances, there is no concern with genotoxicity or carcinogenicity (EFSA, 2014) [8].

[12] NICNAS (2016). Human Health Tier II Assessment for Propionates. https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment-report?assessment_id=771

- **Developmental Toxicity**

In a developmental toxicity study conducted according to OECD TG 414, calcium propionate was fed to pregnant Wistar rats (24 animals/group) and CD-1 mice (25–30 animals/group) during gestational days (GDs) 6–15 at concentrations of 0, 3, 14, 65 or 300 mg/kg bw/day, and to pregnant hamsters (22 animals/group) during GDs 6–10 and pregnant rabbits (22 animals/group) during GDs 6–18 at concentrations of 0, 4, 19, 86 or 400 mg/kg bw/day. In all species, no effects on maternal or fetal survival, or litter size were reported. There were no increases in fetal or skeletal abnormalities in the study. It was concluded that the substance did not cause developmental toxicity and the no observed adverse effect levels (NOAELs) were 300 mg/kg bw/day in rats and mice and 400 mg/kg bw/day in hamsters and rabbits[7,9].

- Observations in Humans

Propionic acid is not a component of the edible fats and oils, but arises in the intermediary metabolism of the body as the terminal three-carbon fragment in form of propionyl coenzyme A in the oxidation of odd-number carbon fatty acids. Oxidation of the side-chain of cholesterol by rat liver mitochondria yields propionate as the immediate product of cleavage[13]. Propionates are metabolized and utilized in the same way as normal fatty acids and even after large doses no significant amounts of propionic are excreted in the urine. *In vitro* propionic acid is completely oxidized by liver preparations to CO_2 and water.

In an adult male, daily oral doses of 6000 mg of sodium propionate rendered the urine faintly alkaline but had no other effect[14]. Solutions of propionate applied to the eye in concentrations up to 15% in humans and up to 20% in rabbits had no irritating effect[15]. Propionic acid is a moderate irritant of skin causing stinging pain and subsequent hyperpigmentation[16]. No sensitization from topical use has been reported, nor has it any

[13] Mitropoulos, K. A. & Myant, N. B. (1965) Biochem. J., 97, 26c; Cited in WHO food Additives Series No. 5, Toxicological Evaluation of Some Food Additives Including Anticaking Agents, Antimicrobials, Antioxidants, Emulsifiers and Thickening Agents. Geneva June 25th to July 4th 1973.

[14] Bässler, K. H. (1959) Z. Lebensmittel. Unters Forsch., 110, 28; Cited in WHO food Additives Series No. 5, Toxicological Evaluation of Some Food Additives Including Anticaking Agents, Antimicrobials, Antioxidants, Emulsifiers and Thickening Agents. Geneva June 25th to July 4th 1973.

[15] Theodore, J. (1950) J.A.M.A., 143, 226; Cited in WHO food Additives Series No. 5, Toxicological Evaluation of Some Food Additives Including Anticaking Agents, Antimicrobials, Antioxidants, Emulsifiers and Thickening Agents. Geneva June 25th to July 4th 1973.

[16] Oettel, H. (1936) Arch. exp. Path. Pharmak., 183, 641; Cited in WHO food Additives Series No. 5, Toxicological Evaluation of Some Food Additives Including Anticaking Agents, Antimicrobials, Antioxidants, Emulsifiers and Thickening Agents. Geneva June 25th to July 4th 1973.

anticoagulant effect[17]. Two male and two female volunteers were treated locally with 0.05 or 0.1% histamine phosphate and inhibition of the reaction by 7.5% or 15% sodium propionate was measured. A moderate potency of about 1/7.5 of that diphenhydramine was found[18]. As noted above, propionate is a normal intermediary metabolite, and a normal constituent of foods[19].

[17] Heseltine, W. W. (1952a) J. Pharm. Pharmacol., 4, 120; Cited in WHO food Additives Series No. 5, Toxicological Evaluation of Some Food Additives Including Anticaking Agents, Antimicrobials, Antioxidants, Emulsifiers and Thickening Agents. Geneva June 25th to July 4th 1973.

[18] Heseltine, W. W. (1952b) J. Pharm. Pharmacol., 4, 577Cited in WHO food Additives Series No. 5, Toxicological Evaluation of Some Food Additives Including Anticaking Agents, Antimicrobials, Antioxidants, Emulsifiers and Thickening Agents. Geneva June 25th to July 4th 1973.

[19] Propionic Acid and Its Calcium, Potassium and Sodium Salts. Seventeenth Report of the Joint FAO/WHO Expert Committee on Food Additives, Wld Hlth Org. Techn. Rep. Ser., 1974, No. 539; FAO Nutrition Meetings Report Series, 1974, No. 53

CONCLUSION

A safety assessment regarding the use of calcium propionate as a component of an antibrowning formulation applied to processed fruits and vegetables was conducted by Dr. Nicholas Skoulis. Dr. Skoulis is an expert in assessing the safety of food ingredients and is highly qualfied to issue a determination regarding the GRAS status of calcium propionate. Dr. Skoulis's assessment is based on publically available safety data for calcium propionate and related compounds and recent safety evaluations from other qualified scientific groups - in particular, the EFSA Panel on Food Additives and Nutrient Souces added to Food (ANS).

For the following reasons, Dr. Skoulis has concluded that calcium propionate is GRAS when used as an antibrowing agent on processed fruits and vegetables.

- Calcium propionate is commonly used in food and, pursuant to 21CFR §184.1121, it has been affirmed as GRAS.
- The Estimated Daily Intake (EDI) for calcium propionate from the antibrowing use is significantly lower than cumulative EDI for this substance.
- The publically available safety studies for calcium, calcium propionate and related compounds clearly indicate that no adverse effects were observed at exposure levels that significantly exceed the EDI for calcium propionate.

It is the opinion of Dr. Skoulis and Wonderful Citrus that other qualified experts would concur with these conclusions.

(b) (6)

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Nicholas P. Skoulis, Ph.D.
Senior Consulting Toxicologist

Part 7. References

https://pubchem.ncbi.nlm.nih.gov/compound/calcium_propionate#section=Names-and-Identifiers

IOM (1997). Calcium. In: Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine (I0M). Washington (DC): National Academy Press (NAP), pp. 71-145. Available from: http://books.nap.edu/openbook.php?isbn=0309063507&paqe=71.

IOM (2011). Dietary Reference Intakes for Calcium and Vitamin D. Washington (DC): National Academy of Science (NAS), Institute of Medicine (I0M), Food and Nutrition Board. Available at: http://www.nap.edu/cataloq.php?record id=13050.

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Thomas, Joseph

From: Eliot Harrison <eharrison@lewisharrison.com>
Sent: Tuesday, August 21, 2018 11:22 AM
To: Thomas, Joseph
Subject: RE: Questions for GRAS Notice GRN 000786
Attachments: GRASN 000786_20180821110214.pdf; US EPA TSCA ChAMP 2007 HPV.pdf; Calcium Dipropionate IUCLID Document.pdf

Hi Dr. Thomas,
Here you go.
Best regards,
Eliot

From: Thomas, Joseph [mailto:Joseph.Thomas@fda.hhs.gov]
Sent: Monday, July 30, 2018 10:47 AM
To: Eliot Harrison
Subject: Questions for GRAS Notice GRN 000786

Dear Mr. Harrison,

Please find attached a letter requesting clarification of several issues with regard to GRN 000786.

Sincerely,

Joseph M. Thomas, Ph.D.
Consumer Safety Officer

Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
U.S. Food and Drug Administration
Tel: 301-796-9465
joseph.thomas@fda.hhs.gov

LEWIS &
HARRISON
Consultants in Government Affairs

2461 South Clark Street
Suite 710
Arlington, VA 22202
telephone 202.393.3903
fax 202.393.3906

August 20, 2018

Joseph M. Thomas, Ph.D.
Consumer Safety Officer
Division of Petition Review (HFS-265)
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5001 Campus Drive
College Park, MD 20740

re: GRAS Notice Number 000786
Calcium Propionate as a Component of an Anti-Browning Formulation
Applied to Processed Fruits
Notifier: Wonderful Citrus, LLC
Your Letter Dated July 30, 2018

Dear Dr. Thomas:

On behalf of Wonderful Citrus, LLC ("WC"), I am responding to the questions and issues from your letter dated July 30, 2018, concerning the above referenced GRAS Notice. Each question/issue and our response is presented below. In addition, revised pages for the GRAS Notice are attached.

Question/Issue No. 1a: Please confirm that 21CFR §184.1081 is the appropriate CFR reference for calcium propionate.

Response: WC believes that the appropriate CFR reference for calcium propionate is 21CFR §184.1221. The reference – 21 CFR §184.1081 – is for propionic acid. Both references are pertinent to this GRAS Notice and are referenced on revised page 00006.1.

Question/Issue No. 2: Please clarify whether the intended use for calcium chloride is on "vegetables" or "processed vegetables" and please comment on the rationale behind extrapolating dietary exposure from this use on vegetables using only data on processed apples.

Response: Wonderful is requesting that the GRAS Notice be modified to only include use of calcium propionate on processed fruits.

Question/Issue No. 3: Please correct the dietary calculations on page 8 and any sections in the submission relying on the resulting value for calcium residue levels.

Response: The correct calculations are on revised pages 00006.1, 00008.1, 000012.1 and 000013.1.

Question/Issue No. 4: Please explain why sodium propionate, calcium propionate and calcium dipropionate should be considered toxicologically equivalent.

Response: Please refer to the middle of page 000018.1 for the basis of toxicological equivalence.

Question/Issue No. 5: Please confirm that the two USEPA High Production Volume references are the same and provide FDA with the document.

Response: WC confirms that the two references are for the same document. A copy of the document is attached.

Question/Issue No. 6: Please provide FDA with the full IUCLID dataset.

Response: A copy of the publically available IUCLID document is attached.

Question/Issue No. 7: Please clarify the oral LD_{50} values in rats for calcium propionate.

Response: Please refer to pages 000018.1 and 000019.1.

Question/Issue No. 8: There are several items regarding the genotoxicity studies that need to be addressed.

Response: Please refer to pages 000019.1 through 000022.1.

Question/Issue No. 9: Please note that all studies spanning 1 year are chronic studies and provide the full primary references.

Response: As noted on page 000023.1, the subject study was actually only 32 weeks. The full primary references are now included.

Question/Issue No. 10: Regarding the safety study in which rats were fed bread containing sodium propionate, please estimate the daily intake of sodium propionate in mg/kg- bw, provide the primary reference and briefly describe a second similar study.

Response: These items are addressed on page 000024.1.

Question/Issue No. 11: Please revise the discussion of the short-term/subchronic studies.

Response: Please refer to the bottom of page 000022.1.

Questions/Issues No. 12: Please provide the primary references for the chronic studies.

Response: These references are included on pages 000025.1 and 000026.1.

Question/Issue No. 13: Please clarify your conclusion regarding the chronic study in the rat.

Response: Please refer to 000026.1.

Question/Issue No. 14: Regarding the Charles River rat study, please indicate if the earlier onset of spontaneous subepithelial basophilic deposits in the renal pelvis among treated rats are an adverse effect and if they are relevant to humans. If not, explain why not.

Response: Please refer to page 000025.1.

Question/Issue No. 15: Please discuss the Owen, et. al. chronic dog study.

Response: Please refer to page 000025.1.

Question/Issue No. 16: Please provide the month and year of Wonderful Citrus' updated scientific literature search for calcium chloride and its ionic components.

Response: Please refer to page 000033.1.

If you have any questions about this response, please contact me at (202) 393-3903, ext. 114 or by e-mail at eharrison@lewisharrison.com.

Sincerely,

(b) (6)

Eliot Harrison
Agent for Wonderful Citrus

Part 2. The Identity, Method of Manufacture, Specifications and Physical and Technical Effect of the Notified Substance

Chemical and regulatory information regarding calcium propionate is presented below.

2.1 Identity

Common or Usual Name: Calcium propionate

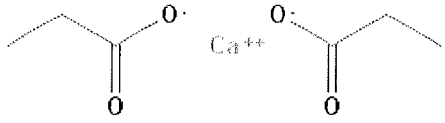
Chemical Name: Calcium propionate

Chemical Abstracts Service (CAS) Number: 4075-81-4

Empirical Formula and Formula Weight: $C_6H_{10}O_4Ca$

Chemical Structure:

Figure: Calcium propionate[1]



Current Regulated Food Uses:

Calcium propionate has been affirmed as Generally Recognized as Safe (GRAS), under 21 CFR §184.1221, when used as an antimicrobial agent, at levels not to exceed good manufacturing practice, in the following foods: baked goods (as defined in 21 CFR §170.3(n)(1)), cheeses (as defined in 21 CFR §170.3(n)(5)) confections and frostings (as defined in 21 CFR §170.3 (n(9)) gelatins, puddings and fillings (as defined in 21CFR 170.3(n)(22)) and jams and jellies (as defined in 21CFR §170.3(n)(28). In addition, propionic acid has been affirmed as GRAS under 21CFR §184.1081 when used as an antimicrobial agent, as defined in 21 CFR §170.3(2) and flavoring agent as defined by 21 CFR §170.3(o)(12) at levels in foods not exceed good manufacturing practice.

2.2 Manufacturing Information and Specifications

The notifier will purchase calcium propionate from suppliers that meet the manufacturing requirements in 21 CFR §184.1221 for calcium propionate or the alternative manufacturing process described in GRAS Notice No. 157. Specifically, calcium propionate is prepared by neutralizing propionic acid with calcium hydroxide or by hydrolyzing propionitrile with calcium hydroxide and then removing ammonia.

[1] https://pubchem.ncbi.nlm.nih.gov/compound/calcium_propionate#section=Names-and-Identifiers

Part 3. Dietary Exposure

3.1 Dietary Exposure from the Proposed Use

Dietary exposure to calcium propionate can result from the consumption of processed fruits that are treated with the antibrowning formulation containing calcium propionate. Since calcium propionate readily dissociates when diluted in water, dietary exposure will occur to calcium and propionate ions.

In a residue study conducted at California Polytechnic State University, residue levels of ascorbate, propionate and chloride were measured after treatment of pre-cut apples. The apples were submerged in the formulation containing these components (5% calcium ascorbate, 1% calcium propionate and 0.2% calcium chloride and then centrifuged and dried. The results are shown in Table 1 below.

Table 1
Average Residue Levels of Ascorbate, Propionate and Chloride
After Treatment with Antibrowning Formulation

Ingredient	Residue Level (mg/kg apple)
Ascorbate	736.18 Standard Deviation: 137.22
Propionate	147.22 Standard Deviation: 27.44
Chloride	29.44 Standard Deviation: 5.49

Although the residue levels of calcium were not assayed, the calcium level can be calculated by assuming that calcium and propionate ions are similarly retained on treated apples. Based on this assumption, the calcium residue is then derived by multiplying the propionate residue levels by the ratio of calcium to propionate in calcium propionate. Since the molar weight of calcium and propionate are 40 g/mol and 73 g/mol, respectively, and there are two moles of propionate per mole of calcium, the weight ratio of calcium to propionate is $40 \div (2 \times 73) = 0.273$. Therefore, the calcium residue is calculated as follows:

Calcium Residue = Propionate Residue on Fruit (147.22 mg/kg fruit) × Ratio of Calcium to Propionate in Calcium Propionate (0.273)

Calcium Residue = 40.1 mg/kg fruit

Based on the residue levels for propionate and calcium (page 8 of this Notice) and the daily intakes for apples and lemons, the EDI for propionate and calcium from the use of the antibrowning formulation is shown below. It is assumed that the residue levels in lemons for propionate and calcium will be the same as those measured and calculated for apples.

Propionate

Child

- Apples:

  (48 g/day) (0.1472 g/1000 g of apples) = 7.0×10^{-3} g/day or 7.0 mg/day

- Lemons

  (3 g/day) (0.1472g/1000 g of lemons) = 4.4×10^{-4} g/day or 0.44 mg/day

Accordingly, the total intake of propionate for children, at the 90th percentile, is 7.4 mg/day +0.44 mg/day = 7.44 mg/day.

Adults

- Apples:

  (112 g/day) (0.1472 g/1000 g of apples) = 1.64×10^{-2} g/day or 16.4 mg/day

- Lemons

  (8 g/day) (0.1472 g/1000 g of lemons) = 1.17×10^{-3} g/day or 1.17 mg/day

Accordingly, the total intake of propionate for an adult, at the 90th percentile, is 16.4 mg/day + 1.17 mg/day = 17.57 mg/day.

Calcium

Child

- Apples:

  (48 g/day) (0.04 g/1000 g of apples) = 1.92×10^{-3} g/day or 1.92 mg/day

- Lemons

  (3 g/day) (0.04 g/1000 g of lemons) = 1.2×10^{-5} g/day or 0.12 mg/day

Accordingly, the total intake of calcium for children, at the 90th percentile, is 1.92 mg/day + 0.12 mg/day = 2.04 mg/day.

Adults

- Apples:

  (112 g/day) (0.04 g/1000 g of apples) = 4.48×10^{-3} g/day or 4.48 mg/day

- Lemons

  (8 g/day) (0.04 g/1000 g of lemons) = 3.2×10^{-4} g/day or 0.32 mg/day

Accordingly, the total intake of calcium for adults, at the 90th percentile, is 4.48 mg/day + 0.32 mg/day = 4.80 mg/day.

3.2 Dietary Exposure from Existing Uses

Dietary intake values for calcium and propionate have been reported in previously submitted GRAS Notices and are summarized below.

Propionate

The daily intake of calcium propionate was calculated in GRAS Notice No. 157, (https://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm264105.pdf). According to this notice, the average daily intake of calcium propionate is 220 mg/person/day (page 15 of the GRAS Notice), which is equivalent to 180 mg/person/day of propionate. The EDI for propionate, from the use of calcium propionate as an antibrowning agent for processed fruits and vegetables, at the 90th percentile, is 7.44 mg/day (child) and 17.57 mg/day (adult). Consequently, the EDI for propionate, resulting from the antibrowning use, will be less than 10% of the average daily intake of propionate from all food uses.

Calcium

The dietary intake of calcium was presented in GRAS Notice No. 634, https://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm505252.pdf. The notice reported that for the U.S. population, age 1 year and older, the *per user* intake of calcium at the 90th percentile is 1,936 mg/day (see page 26 of the Notice). The EDI for of calcium, from the use of calcium propionate as an antibrowning agent for processed fruits and vegetables, at the 90th percentile, is 1.92 mg/day (child) and 4.80 mg/day (adult). Consequently, the antibrowning use results in a daily intake that is less than 1.0% of the total daily intake of calcium at the 90th percentile.

Part 6. Safety Evaluation and Basis for Our Conclusion of GRAS Status

As noted above, calcium propionate, when dissolved in water, will dissociate into calcium and propionate ions. Accordingly, the safety assessment focuses on both of these ions as well as calcium propionate.

Acceptable Levels of Calcium Based on Human Data

The Health and Medicine Division (HMD, formerly the Institute of Medicine) of the National Academy of Sciences established an Upper Limit (UL) for calcium of 2,500 mg/person/ day from all sources (e.g., food and supplements) for all age groups, including pregnant or lactating women, based on the risk for hypercalcemia and renal insufficiency at intakes ranging from 4,000 to 5,000 mg of calcium/person/day and greater (IOM, 1997)[1]. A UL for infants aged 0 to 12 months could not be established due to insufficient data. The IOM/HMD was subsequently asked to review new data and, in 2011, published updated ULs (IOM, 2011)[2].

For infants, new data were available regarding calcium excretion that suggested that infants can tolerate intakes of up to approximately 1,750 mg/day. Thus, a no-observed-adverse-effect level (NOAEL) of 1,750 mg/day was established. For infants 0 to 6 months of age, an uncertainty factor of 2 was applied to account for body weight differences and the UL was set at 1,000 mg/day. The UL for infants, aged 7 to 12 months, was set at 1,500 mg/day since an increased capacity to handle calcium will accompany increased body size.

The UL for children aged 1 through 8 was not changed and remains at 2,500 mg/day, whereas the UL for children aged 9 to 13 years and adolescents aged 14 to 18 years, including pregnant and lactating adolescents, was raised by 500 mg/day to 3,000 mg/day to account for the increase in bone accretion and likely accompanying increases in tolerated intakes. For adults, although the IOM/HMD recognized that hypercalcemia was an adverse outcome, they noted it was a disease state and should not be considered appropriate for the derivation of ULs for the normal, healthy population. Kidney stone formation was selected as the indicator, and an UL of 2,000 mg/day

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[1] IOM (1997). Calcium. In: *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride.* Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine (IOM). Washington (DC): National Academy Press (NAP), pp. 71-145. Available from: http://books.nap.edu/openbook.php?isbn=0309063507&paqe=71.

[2] IOM (2011). *Dietary Reference Intakes for Calcium and Vitamin D.* Washington (DC): National Academy of Science (NAS), Institute of Medicine (IOM), Food and Nutrition Board. Available at: http://www.nap.edu/cataloq.php?record id=13050.

was set for adults aged 51 to 70 and greater than 70 years based on increased risk of kidney stone formation at higher intakes.

It was noted by the IOM/HMD committee that "intakes of calcium from food do not readily result in excess intakes and are not associated with adverse effects; rather, the adverse effects appear to be a function of calcium supplementation added to baseline intake" (IOM, 2011)[2]. Although kidney stone formation does occur in younger adults, the IOM/HMD committee noted that it does not appear to be correlated with calcium supplement use, and thus established an UL of 2,500 mg/day for adults, including pregnant and lactating women, aged 19 to 30 and 31 to 50 years using an interpolation approach based on the mid-point between the UL for adolescents and persons greater than 50 years of age.

The European Commission's Scientific Committee on Food (SCF) established a UL of 2,500 mg/person/day from all sources for all age groups, including pregnant or lactating women, based on no adverse effects observed at this intake level in human studies (SCF, 2003)[3].

In summary, the biological and toxicological effects related to calcium intake have been extensively evaluated in contemporary reviews conducted by both the National Academy of Sciences (IOM, 2011) and a recent study conducted by the European Food Safety Authority (EFSA, 2012). As discussed above, based on calcium excretion in young children and formation of kidney stones in older children and adults, the IOM/HMD established tolerable upper limits (ULs) for infants 0-6 months (1,000 mg/day), infants 6-12 months (1,500 mg/day), children 1– 8 years (2,500 mg/day), adolescents 9-18 years (3,000 mg/day), adults 19 – 50 years (2,500 mg/day), and older adults 51+ years (2,000 mg/day). The IOM/HMD concluded that there were insufficient data to determine a UL based on other effects, including increased risk of cardiovascular disease (CVD) among post-menopausal women and older men. EFSA's most recent evaluation (2012) reached similar conclusions on the lack of adverse associations between calcium intake and CVD, as well as other health endpoints, but did not believe the available

[3] SCF (2003). *Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Calcium* (expressed 4 April 2003). (SCF/CS/NUT/UPPLEV/64 Final). European Commission, Scientific Committee on Food (SCF). Available at:https://ec.europa.eu/food/sites/food/files/safety/docs/sci-com_scf_out194_en.pdf.

evidence required a revision of the UL of 2,500 mg/day for adults as previously established by the Scientific Committee on Food (SCF) in 2003.

The literature published since the IOM review in 2011 did not indicate any new new data or assessments that would alter the significant scientific consensus presented in the IOM (2011) or the EFSA (2012) reviews.

Toxicological Studies

- Overview

Toxicological studies have been conducted with propionic acid, sodium propionate, calcium propionate and calcium dipropionate. All of these substances should be considered toxicogically equivalent; therefore, the data on propionic acid, sodium propionate and calcium dipropionate can be bridged to calcium propionate. Propionic acid[4], sodium propionate, calcium propionate[5] and calcium diproprionate "should be considered toxcologically equivalent" as propionic acid and its salts are soluble in water and would dissociate to the propionate anion and respective cations. The oral LD_{50} for calcium propionate is reported to be 3920 to >5000 mg/kg (rats) and 3340 mg/kg in mice, sodium propionate has an oral LD_{50} of 5100 mg/kg in mice[6,7] and propionic acid reported as 2600 mg/kg[8] .

Propionic acid, sodium propionate, and calcium propionate have demonstrated low acute toxicity after oral administration to mice or rats (calcium propionate Oral LD_{50} 3340 mg/kg, mice; sodium propionate Oral LD_{50} 5100 mg/kg, mice). Several assays for mutagenicity of propionic acid and calcium and sodium propionate were negative. Investigations of the teratogenicity of calcium propionate in were negative[9]. Long-term feeding studies of propionic acid and calcium propionate have not been reported.

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[4] Propionic acid, PubChem CID 1032; https://pubchem.ncbi.nlm.nih.gov/compound/propionic_acid#section=Top
[5] Calcium propionate, PubChem CID 19999; https://pubchem.ncbi.nlm.nih.gov/compound/calcium_propionate#section=Top
[6] Hara, S., T. Shibuya, K. Yakazu, T. Kobayashi, R. Takahashi, T. Takeuchi, and K. Tokizaki. 1963. Studies of pharmacological and toxic actions of propionates: examination of general pharmacological actions and toxicity of sodium- and calcium propionates. Tokyo Ika Daigaku Zasshi 21:261-302
[7] US EPA High Production Volume (HPV) Chemical Challenge Program, Summary of Existing Data, Proposed Test Plan and Rationale for Calcium Dipropionate (CASRN 4075-81-4) 201-16574B. Prepared by MorningStar Consulting, Inc. for OM Group, Inc. April 24, 2007.
[8] Weissburger, LH and Harris, PL. J. Biol. Chem., 151:543. 1943.

However, a long-term feeding study conducted with sodium propionate showed no adverse effects in rats and, as noted above, sodium propionate can be considered toxicologically equivalent to calcium propionate.

Based on the review of the data, the conclusion is that there is no evidence in the available information on propionic acid, calcium propionate, and sodium propionate that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that are now current or that might reasonably be expected in the future, this conclusion is consistent with the conclusions published by the Select Committee on GRAS Substances[9].

- Individual Toxicology Studies

Acute Toxicity

The oral LD_{50} in rats for calcium propionate ranged from 3920 to >5000 mg/kg[6,9]. The 4 hr. acute inhalation LC_{50} in rats is >5.4 mg/L (calcium propionate) and the acute dermal LD_{50} in rabbits is 500 mg/kg. Calcium dipropionate is reported to be non-irritating to either the eyes or the skin[7].

Genotoxicity

In the bacterial mutation assay (Ames Test), calcium dipropionate was evaluated in the following *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538, with and without S9 metabolic enzymes. Under the conditions of the assay, calcium dipropionate and was found to be non-mutagenic[10].

In a bacterial point mutation assay, sodium and calcium propionate were assayed for gene mutation with six *Salmonella typhimurium* strains (TA92, TA94, TA98, TA100, TA1535 and TA1537), in the absence or presence of a rat liver metabolic activation system.

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[9] Calcium Propionate; Dilaurryl thiodipropionate; Propionic acid; Sodium propionate; Thiodipropionic acid. SCOGS Report No.: 79, NTIS Accession No.: PB80104599, 1979.

[10] Ishidate M Jr, Sofuni T, Yoshikawa K, Hayashi M, Nohmi T, Sawada M, Matsuoka A. Primary mutagenicity screening of food additives currently used in Japan. Food Chem Toxicol. 1984 Aug; 22(8):623-36.

The maximum concentrations of sodium and calcium propionate studied were 5 and 10 mg/mL, respectively. Both chemicals tested negative in the assay[11].

In a separate bacterial point mutation assay, calcium propionate was assayed for gene mutation with *S. typhimurium* strains (TA1535, TA1537 and TA1538) and for gene conversion with *Saccharomyces cerevisiae* strain D4 in the absence or presence of exogenous mouse, rat and monkey liver metabolic activation systems. Negative results were obtained, but it is noted that the study had poorly reported concentration levels and experimental designs[12].

In a separate study, calcium propionate was tested for mutagenicity in *S. typhimurium* strains G-46 and TA1530 and for recombinogenic properties in *S. cerevisiae* strain D3. Negative findings were reported, but it is noted that the study had poorly reported concentration levels and experimental design [12].

Ishidate et al. (1988) undertook a review of 951 chemicals, of which included 242 food additives that included calcium propionate and sodium propionate; all of the chemicals had been assayed for their potential to induce clastogenicity when tested in the *in vitro* Chinese Hamster Lung Cell (CHL, V79 cells) Test, with and without metabolic activation (S9)[13]. Treatments were performed for 24 and 48 hours at three does-levels, with sodium- and calcium propionate being dosed at the maximum level of 2 mg/ml (10 mM). Results for sodium propionate demonstrated negative findings; for calcium propionate an equivocal clastogenic response was observed.

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[11] Ohta T. et al.: Mutat. Res. 77, 21–30 (1980).

[12] Litton Bionetics, Inc. 1973. Summary of mutagenicity screening studies: host-mediated assay; cytogenetics; dominant lethal assay: compound FDA 71-36, calcium propionate. Prepared under DHEW contract no. FDA 71-286. Kensington, Md. 95 pp. unpublished report in EFSA (2014). Scientific Opinion on the Re-Evaluation of Propionic Acid (E280), Sodium Propionate (E281), Calcium Propionate (E282) and Potassium Propionate (E283) as Food Additives. EFSA Panel on Food Additives and Nutrient Sources Added to Food (ANS). EFSA Journal 12(7); 3779, 2014.

[13] Ishidate Jr., M., Harnois, MC, and Sofuni, T. A Comparative analysis of data on the clastogenicity of 951 Chemical Substances Tested in Mammalian Cell Cultures. Mutation Research, 195:151-213, (1988).

However, typical exposure and harvest times for CHL V79 cells are in the order of about 6 hours and usually not exceeding 24 hours, and since the equivocal results were only observed at the 48 hour treatment, the treatment is considered excessive and the results are considered not biologically relevant.

Calcium dipropionate was negative in the cytogenetic and dominant lethal assays. Propionic acid was negative in a micronucleus test. In the *in vivo* mouse micronucleus assay studies, calcium dipropionate showed no chromosomal aberrations in rat bone marrow cells and no dominant lethal mutations were observed[14].

In a bone marrow chromosomal aberration assay, rats were administered 0, 50, 500 or 5000 mg/kg bw of calcium propionate by oral gavage as a single dose (59 animals) or daily for five consecutive days (18 animals). The animals were euthanized six, 24 or 48 hours after dosing in the single treatment groups and six hours after the last dose in the repeated treatment groups. Chromosomal aberration and mitotic index were determined in this study and calcium propionate did not induce statistically significant increases at any treatment level[15,16].

In a rat bone marrow cytogenetic assay, sodium propionate was tested for genotoxicity effects and negative findings were reported. No further details were provided for the study[17].

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[14] Litton Bionetics, 1974a. Summary of mutagenicity screening studies host-mediated assay cytogenetics dominant lethal assay contract FDA 71-268, compound FDA 71-36, calcium propionate. LBI Project 2446. March 1973, revised September 1974. Cited in EFSA Journal 12(7):3779, 2014

[15] IUCLID Dataset (2000). Calcium Dipropionate CAS# 4075-81-4. European Commission – European Chemicals Bureau, 18-February 2000.

[16] EFSA (2014). Scientific Opinion on the Re-Evaluation of Propionic Acid (E280), Sodium Propionate (E281), Calcium Propionate (E282) and Potassium Propionate (E283) as Food Additives. EFSA Panel on Food Additives and Nutrient Sources Added to Food (ANS). EFSA Journal 12(7); 3779, 2014.

[17] Kawachi, T., Yahagi, T., Kada, T., Tazima, T., Ishidate, M., Sasaki, M. & Sugiyama, T. (1980b) Cooperative programme on short-term assays for carcinogenicity in Japan. In: Montesano, R., Bartsch, H. & Tomatis, L., eds, Molecular and Cellular Aspects of Carcinogen Screening Tests (IARC Scientific Publications No. 27), Lyon, IARC, pp. 323–330.

In a host-mediated assay, male mice were administered 50, 500 or 5000 mg/kg bw of calcium propionate by oral gavage as a single dose or daily for five consecutive days. Positive and negative control groups were included in both single and repeated treatments. The *S. typhimurium* strains (G-46 and TA1530) and *S. cerevisiae* strain D3 were used as indicator organisms for inducing reverse mutation and mitotic recombination, respectively. In the single dose treatment, all animals received 2 mL of the indicator organisms (3×10^8 cells for *S. typhimurium* and 5×10^8 cells for *S. cerevisiae*) immediately after treatment by intraperitoneal (i.p.) injection. The animals were euthanized three hours later with the indicator organisms removed from the peritoneal cavity and plated for colony scoring. Results indicated a non-dose-related increase in the reversion frequency of *S. typhimurium* strain G-46. Therefore, the results were considered not biologically relevant. Negative findings were reported for strains TA1530 and D3[15].

In a dominant lethal assay, male rats were administered 50, 500 or 5000 mg/kg bw of calcium propionate by oral gavage as a single dose, or daily for five consecutive days. Positive and negative control groups were included in both single and repeated treatments. Following treatments, the animals were sequentially mated with two untreated virgin females, five days/week for eight weeks. At the end of the treatment every week, the females were replaced with two untreated virgin females. The treated females were removed from the males, housed separately and euthanized 14 days after separation. The uteri were analyzed for early and late fetal deaths and total implantations. Negative findings were reported in the study[7].

Short-term/Subchronic Studies

Repeat dose studies with calcium propionate, sodium propionate and propionic acid were conducted in rats, dogs and monkeys with study periods ranging from 4 weeks to 90 days and exposure levels ranging up to 3320 mg/kg/day. No abnormalities in clinical or hematological examinations were observed. Changes in the forestomach (e.g., hyperkeratosis and hyperplasia) were observed. These changes were observed to occur equally with calcium and sodium propionate, but were more marked with exposure to propionic acid.

The changes were largely reversible, attributed to the acidity of the compound, and were not related to any systemic toxicity of the compound. The no-observable effect-level was considered to be 3320 mg/kg/day[18].

In a repeat dose toxicity study, rats were fed 0, 830 or 2490 mg/kg bw/day of sodium or calcium propionate in their diet for 3–4 weeks. The only endpoint measured in this study was growth and no effect was observed[19].

Wistar rats were maintained on a normal diet, or diet consisting of 75% bread that was baked with the addition of a 50-fold amount of four bread additives and bleached flour for 32 weeks (note: Grahma & Grice refer to the study as a 52 week study but it only ran for 32 weeks – no reason for the change from a 52-week study to a 32-week study was given)[20]. Sodium propionate at a concentration of 5% was one of the additives. Although it would not be possible to determine the attribution of effects given the complex mixture of substances in this study, no clinical or pathological effects were observed. Therefore, the substance was concluded to not cause toxic effects. Due to the lack of consistency with previous work, Graham & Grice (1954) conducted a second feeding study where the rats were fed uncooked bread, as the first study the bread was baked and the high temperature of baking resulted in a strong odor of propionate as well as the possibility that the high temperatures would have removed a portion of the propionate. Therefore, based on a combination of a palatability issue as well as a potential for unreliable concentrations of propionate in the bread, the second study was undertaken. The second study spanned 32 weeks and the first two weeks the uncooked breads had a lower consumption rate but by week 7 out to week 32 the food consumption stabilized.

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[18] Altman H-J and Grunow, W. 1988a. Ergeb. Neuer. Fuetterungsvers. m.Propions.u.i.Salzen" unpubl. Report Fed. Health Agency (BGA Berlin ,'88). As cited in IUCLID (2000); Altman H-J. and Grunow, W., 1988b. Arbietspapier zur Tox. V. Propions. U.i. Ca-, K-, und Na-Saltze, unpubl. Report Fed Health Agency, BGA Berlin,88; and Harshbarger, K.E., 1942. Report of a study on the toxicity of several food preserving agents. J. Dairy Sci. 25:169-174. Also cited and interpreted in FASEB (1979). Were all cited in US EPA HPV Program document, April 24, 2007.

[19] Harshbarger K.E.: J.Diary Science 25, 169–174 (1942). As cited in IUCLID (2000) Calcium Dipropionate CAS# 4075-81-4. European Commission – European Chemicals Bureau, 18-February 2000.

[20] Graham, WD and Grice, HC. Chronic Toxicity of Bread Additives to Rats. Part II. J. Pharm. Pharmacol. 7:126-134, 1955

The estimated exposures to sodium propionate were as follows: Diet with 0.1% sodium propionate the dose was between 43 and 51 mg/kg-bw; and the diet with with 5.0% sodium propionate resulted in an ingested dose between 2,091 to 2,519 mg/kg-bw (calculated by reviewer (Dr. Skoulis)) using bodyweights and ingestion rate from weeks 7 and 32). The high concentrations of chlorine dioxide, polyoxyethylene (8) monostearate, sodium propionate, and antioxidants had no detectable effect on hemoglobin levels in the blood, organ weights, or on the histopathology of the tissues[26].

In a separate study, Wistar rats (five animals/sex/group) were fed 0 or 40000 ppm (approximately 3320 mg/kg bw/day) of calcium propionate in their diet for four (females) and eight (males) weeks. Following four weeks of oral exposure to the chemical, the treated animals showed slightly thickened limiting ridge in the forestomach and more pronounced hyperkeratosis and hyperplasia of mucosa. More pronounced lesions were observed in the forestomach after eight weeks of exposure. The effects were reversed following an eight-week treatment-free period[16].

In a repeated dose toxicity study in beagle dogs, calcium propionate at concentrations of 0, 14500 or 43500 ppm in the diet was fed to the animals for 90 days. Diarrhea and vomiting were observed in all animals at the highest concentration and one animal in the 14500 ppm group. (NOAEL 14500 ppm approximately equal to 260 mg/kg bw) Spontaneous epithelial hyperplasia of the esophageal mucosa was observed in all groups and was concluded to be not related to treatment. No further details were provided[18].

Venter et al. (1990) investigated the effect of propionate to facilitate the beneficial metabolic effects of dietary fiber. They fed 12 male baboons a western diet with or without 2% propionate or the soluble dietary fiber concentrate, 5% konjac-glucomannan (K-GM) for a period of 9 wks. As indicated sodium propionate was fed at a concentration of 2 % which was equivalent to 420 mg/kg bw/day in the diet for nine weeks. Hematological and liver effects were studied and no toxic effects were observed.

Propionate appeared to actuate the beneficial effects of increased dietary fiber in the diet that was characterized by an increase in high density lipoproteins, decrease in triglycerides, and also decreasing circulating fatty acids[21].

Long-term Toxicity Studies

In a chronic study conducted with Charles River CD rats (40 sex/group), the test animals were fed 2.05% of sodium propionate in the diet (equivalent to 1025 mg/kg-bw/day) for 104 weeks. No adverse effects on bodyweight gain, food consumption, hematology, blood chemistry, organ weights or mortality was observed when compared to control rats receiving a basal diet. There was an increased incidence and earlier onset of spontaneous subepithelial basophilic deposits in the renal pelvis among treated rats. No other histological findings of significance were mentioned. The findings of increased incidence of subepithelial basophilic deposits in the renal pelvis in a few of the treated rats raises the question of biological relevance as this is considered part of the aging process in rats and while there appeared to be an increased incidence and a somewhat earlier onset over control animals this could be the result of an observed increase in the urine output in the treated animals. It should be noted that no other histopathological findings were indicated in the kidney, further supporting the fact that this is part of the normal aging process and is not considered relevant to humans. The organs evaluated by histopathology were not mentioned in detail[22].

Owen et al. (1978) treated beagle dogs for two-years with 5.13% sodium propionate or 2.5, 5.0, or 10.0% monosodium glutamate (MSG). All animals appeared normal throughout the entire dosing period and interim sacrafices after 90-days showed no abnormalities. Results at the end of the study showed no differences in food consumption, bodyweight changes, or hematological/clinical chemistry parameters. The only finding were foci of mineralization in the lumen of medullary tubules in a majority of the test animals including untreated animals; however, the treatment with sodium propionate or MSG did not increase the incidence of this

[21] Venter, CS., Vorster, HH., and VanDerNest, DG. Comparison Between Physiological Effects of Konja-Glucomannan and Propionate in Baboons Fed "Western" Diets. The Journal of Nutrition 120:1046-1055, (1990).
[22] Owen, G., Cherry, CP., Prentice, DE., and Worden, AN. The Feeding of Diets Containing up to 4% Monosodium Glutamate to Rats for 2 Years. Toxicology Letters, 1:221-226 (1978).

finding. According to the study author, focal mineralization in medullary tubules are a common finding in kidneys of beagles maintained in the laboratory. In addititon urinary output and sodium excretion was observed to be slightly increased but the ability to concentrate the urine was unaffected[23]. The results of the beagle dog study are consistent with Owen's previous work in rats[22].

In a lifetime study conducted with an analogue chemical, propanoic acid, male Wistar rats (30 animals/group) were administered this substance in their diet at doses of 0, 264 or 2640 mg/kg-bw/day for 20 weeks or for their lifetime. Ten animals from each group were euthanized at week 20 and the remaining animals were fed with their respective diets until death. No treatment-related effects were observed in the animals treated at 264 mg/kg-bw/day. In the animals treated at 2640 mg/kg- bw/day, forestomach epithelial changes such as hyperplasia and hyperkeratosis were observed at week 20. The other permanent effects included hyperplasia with ulceration, dyskeratosis and papillomatous elevations.

One animal euthanized two years after treatment had hyperplasia with ulceration and unspecified 'carcinomatous changes' along with erosive changes in the glandular region of the stomach[24]. NICNAS concluded that the effects observed were due to chronic irritation and inflammation and the associated hyperplastic proliferative repair response. It should be noted that only forestomach lesions related to chronic irritation were reported. Humans lack a forestomach although some scientists argue that the mouth, pharynx, and esophagus are surrogates for a forestomach. However, the combination of a non-genotoxic compound that is irritating supports this reviewer's position that the conclusion by NICNAS is valid and that the study findings are not relevant to humans.

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[23] Owen, G., Cherry, CP., Prentice, DE., and Worden, A.N. The Feeding of Diets Containing up to 10% Monosodium Glutamate to Beagle Dogs for 2 Years. Toxicology Letters, 1:217-210, (1978).

[24] NICNAS (2016). Human Health Tier II Assessment for Propionates. https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment-report?assessment_id=771

It should also be noted that the EFSA Panel that evaluated propionic acid and the propionates (sodium propionate, calcium propionate and potassium propionate) indicated that, for these substances, there is no concern with genotoxicity or carcinogenicity (EFSA, 2014)[16].

Developmental Toxicity

In a developmental toxicity study conducted according to OECD TG 414, calcium propionate was fed to pregnant Wistar rats (24 animals/group) and CD-1 mice (25–30 animals/group) during gestational days (GDs) 6–15 at concentrations of 0, 3, 14, 65 or 300 mg/kg bw/day, and to pregnant hamsters (22 animals/group) during GDs 6–10 and pregnant rabbits (22 animals/group) during GDs 6–18 at concentrations of 0, 4, 19, 86 or 400 mg/kg bw/day. In all species, no effects on maternal or fetal survival, or litter size were reported. There were no increases in fetal or skeletal abnormalities in the study. It was concluded that the substance did not cause developmental toxicity and the no observed adverse effect levels (NOAELs) were 300 mg/kg bw/day in rats and mice and 400 mg/kg bw/day in hamsters and rabbits[7,9].

- Observations in Humans

Propionic acid is not a component of the edible fats and oils, but arises in the intermediary metabolism of the body as the terminal three-carbon fragment in form of propionyl coenzyme A in the oxidation of odd-number carbon fatty acids. Oxidation of the side-chain of cholesterol by rat liver mitochondria yields propionate as the immediate product of cleavage. Propionates are metabolized and utilized in the same way as normal fatty acids and even after large doses no significant amounts of propionic are excreted in the urine. *In vitro* propionic acid is completely oxidized by liver preparations to CO_2 and water[25].

[25] Mitropoulos, K. A. & Myant, N. B. (1965) Biochem. J., 97, 26c; Cited in WHO food Additives Series No. 5, Toxicological Evaluation of Some Food Additives Including Anticaking Agents, Antimicrobials, Antioxidants, Emulsifiers and Thickening Agents. Geneva June 25th to July 4th 1973.

In an adult male, daily oral doses of 6000 mg of sodium propionate rendered the urine faintly alkaline but had no other effect[26]. Solutions of propionate applied to the eye in concentrations up to 15% in humans and up to 20% in rabbits had no irritating effect[27]. Propionic acid is a moderate irritant of skin causing stinging pain and subsequent hyperpigmentation[28]. No sensitization from topical use has been reported, nor has it any anticoagulant effect. Two male and two female volunteers were treated locally with 0.05 or 0.1% histamine phosphate and inhibition of the reaction by 7.5% or 15% sodium propionate was measured. A moderate potency of about 1/7.5 of that diphenhydramine was found[29]. As noted above, propionate is a normal intermediary metabolite, and a normal constituent of foods[30].

[26] Bässler, K. H. (1959) Z. Lebensmittel. Unters Forsch., 110, 28; Cited in WHO food Additives Series No. 5, Toxicological Evaluation of Some Food Additives Including Anticaking Agents, Antimicrobials, Antioxidants, Emulsifiers and Thickening Agents. Geneva June 25th to July 4th 1973.

[27] Theodore, J. (1950) J.A.M.A., 143, 226; Cited in WHO food Additives Series No. 5, Toxicological Evaluation of Some Food Additives Including Anticaking Agents, Antimicrobials, Antioxidants, Emulsifiers and Thickening Agents. Geneva June 25th to July 4th 1973.

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CONCLUSION

A safety assessment regarding the use of calcium propionate as a component of an antibrowning formulation applied to processed fruits was conducted by Dr. Nicholas Skoulis. Dr. Skoulis is an expert in assessing the safety of food ingredients and is highly qualfied to issue a determination regarding the GRAS status of calcium propionate. Dr. Skoulis's assessment is based on publically available safety data for calcium propionate and related compounds and recent safety evaluations from other qualified scientific groups - in particular, the EFSA Panel on Food Additives and Nutrient Souces added to Food (ANS).

For the following reasons, Dr. Skoulis has concluded that calcium propionate is GRAS when used as an antibrowing agent on processed fruits:

- Calcium propionate is commonly used in food and, pursuant to 21CFR §184.1221, it has been affirmed as GRAS.
- The Estimated Daily Intake (EDI) for calcium propionate from the antibrowing use is significantly lower than cumulative EDI for this substance.
- The publically available safety studies for calcium, calcium propionate and related compounds clearly indicate that no adverse effects were observed at exposure levels that significantly exceed the EDI for calcium propionate.

It is the opinion of Dr. Skoulis and Wonderful Citrus that other qualified experts would concur with these conclusions.

(b) (6)

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Literature Search

An updated, comprehensive literature search and evaluation for use in the safety evaluation of calcium propionate and its ionic components was conducted on September 17, 2017. The following databases were searched.

- PubMed
- ToxPlanet (ChemExpert, ReproExpert, Toxline®Special, RTECS, HDSB®, ChemSpider, EFSA, IARC)
- GRAS Substance Database
- OECD Screening Information
- ECHA BPD/BPR/REACH Database

U.S. EPA High Production Volume (HPV) Chemical Challenge Program

201-16574B

SUMMARY OF EXISTING DATA, PROPOSED TEST PLAN AND RATIONALE FOR CALCIUM DIPROPIONATE (CASRN 4075-81-4)

Prepared by

MorningStar Consulting, Inc.

on behalf of

OM Group, Inc.

The Sponsoring Company

DATE: APRIL 24, 2007

TABLE OF CONTENTS

INTRODUCTION

The following document includes a test plan and a summary of existing data for calcium salt of propionic acid (Ca dipropionate) [CASRN 4075-81-4]. The information provided in this document and the attached dossier of robust summaries meets the requirements under the U.S. High Production Volume (HPV) Chemical Challenge. Ca dipropionate is one of 19 sponsored chemicals organized under the Metal Carboxylates Coalition (The Coalition), an HPV testing consortium managed by the Synthetic Organic Chemical Manufacturers Association's (SOCMA) VISIONS Department. Ca dipropionate is sponsored by the OM Group (OMG).

USE PATTERNS AND REGULATORY BACKGROUND

Ca dipropionate, [$2(CH_3CH_2COOH^-)$ Ca^{2+}] is a metal carboxylic acid, a salt of calcium and the alpha monocarboxylic acid, propionic acid. Ca dipropionate is used in variety of ways including as a common food and feed additive, as a pesticide active ingredient (fungicide), and as an inert ingredient in pesticides. Since 1979 the Code of Federal Regulations (CFR) has listed Ca dipropionate (21 CFR 182.3221), propionic acid [21 CFR 182.3081] and the sodium salt, Na propionate [21 CFR 182.3784] as a generally recognized as safe (GRAS) chemical preservative in food (FASEB 1979). Products such as these are commonly used as additives in cheese and milk products, meats, beverages and other consumer products.

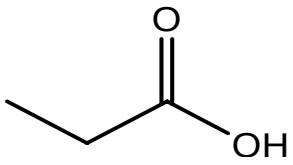
The EPA Office of Pesticide Programs (OPP) recently released a Final Rule exempting from tolerance the residues of these three chemicals in raw agricultural commodities pursuant to section 408 of the Federal Food, Drug and Cosmetic Act (FFDCA). The tolerance for propionic acid (also known as propanoic acid)[1] is found in 40 CFR Part 180 and was announced in the Federal Register August 4, 2004 (Vol. 69, No. 149). Under this exemption, Ca dipropionate residues are permitted to be present in, or added to, any agricultural product with no restriction on the amount of residue present. This tolerance exemption provides a recent affirmation of the status of Ca dipropionate and propionic acid as GRAS. An excerpt of the August 4 *Federal Register* explains:

> *Based on "…the low potential for toxicity of propanoic acid [a synonym for propionic acid] and its calcium and sodium salts for the oral route of exposure, that humans of all ages are highly exposed to propanoic acid from natural sources, and that the human body has a known pathway for metabolizing propanoic acid…EPA concludes that exempting propanoic acid, and its calcium and sodium salts from the requirements of a tolerance will be safe for*

the public, including infants and children" (Fed. Reg. Aug 4, 2004, Vol. 69, No. 149).

These same compounds have also been evaluated internationally. The safety of these compounds for use in food has been evaluated several times by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Propionic acid and three of its simple salts (Ca^{2+}, Na^{+}, K^{+}) have been established internationally as common food additives used as mold inhibitors, preservatives, and flavoring agents. The JECFA concluded as recently as 1997 that there is no safety concern for these compounds at the current levels of use and that their Acceptable Daily Intake (ADI) need not be limited. Propionates are metabolized and utilized in the same way as a normal fatty acid (JECFA, 1962). The toxicology evaluation for these compounds concluded that there is no reason to believe that the propionic acid differs toxicologically from its calcium and sodium salts (JECFA, 1966).

Figure 1: Structures of Ca dipropionate



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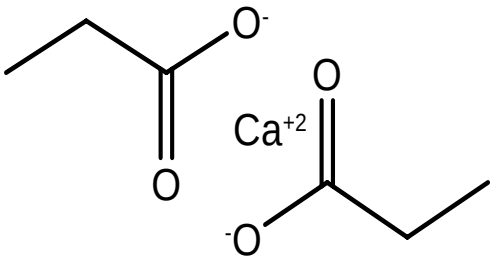

B

A) Propionate (as the free acid)

B) Ca dipropionate

Ca dipropionate is considered a "simple" salt due to the presence of calcium. This divalent metal action is not considered toxicologically significant. Calcium is an essential element that is absorbed mainly through active transport. The amount absorbed is regulated according to the current needs of the body with the participation of vitamin D, parathormone, and calcitonin. Normal calcium absorption requires the presence of vitamin D, a Ca-binding protein and amino acid (lysine and L-arginine).

One characteristic of Ca dipropionate and other metal carboxylates is that they are ion pairs, which readily dissociate in water. The dissociation constants show that at the low pH of the stomach, the important moieties from a toxicological standpoint are the unionized free acid and ionized metal. Because of this, mammalian toxicity data for the free acid, or that for a simple salt of the acid (e.g., the sodium salt or the calcium salt), can serve as surrogate data for the acid component of respective metal carboxylates such as Ca dipropionate. Table 1 shows how similar the acute toxicity data is for the salt, Ca dipropionate, and

the free acid, propionate. Under these conditions, the contribution of the metal ion (Ca^{+2}) to any observed toxicity is considered minimal or insignificant. This is supported by the treatment of the acid and the Ca and Na salts as equivalent in the recent Exemption of Tolerance decision by the EPA (Fed. Reg. Aug 4, 2004, Vol. 69, No. 149).

Table 1. Comparison of acute toxicity values for Ca dipropionate and its carboxylic acid, propionate

Acute Mammalian Toxicity[a]	**Ca dipropionate**	**Propionate**
Acute oral toxicity (LD50 in mg/kg bw)	3920-4380	2600-4290
Acute inhalation toxicity (LC50 in mg/L)	>5.4	>4.9
Acute dermal toxicity (LD50 in mg/kg bw)	500	500

[a] See Table I

For this reason the data for the free acid, propionate, are clearly delineated as supporting data and summarized and referenced in the appropriate "Remarks" sections for each data element in the robust summaries of Ca dipropionate. These data are also presented in Tables I.

EXISTING DATA FOR CA DIPROPIONATE – SUMMARY

Physicochemical Properties

Available physicochemical property data for this compound and its carboxylic acid are shown in Table I and briefly summarized below.

Physicochemical properties are well characterized for Ca dipropionate. Data for all five physicochemical endpoints are available for either Ca dipropionate or propionic acid (Table I) (IUCLID 2000b).

Melting Point

The melting point was not applicable (NA) for the Ca salt, but was reported as 22.4^{o}C for the acid.

Boiling Point

Boiling point was evaluated in a GLP study in 2004, but could not be measured under the test conditions (RCC 2003). The reported values for the boiling point of propionic acid are 140.7 to 141.6^{o}C (IUCLID 2000b).

Density

Density for Ca dipropionate is reported as 400 mg/m^3 (IUCLID 2000a)

Vapor Pressure

Vapor pressure was not considered applicable for Ca dipropionate, but was reported as 5 hPa at 20^{o}C for the acid (IUCLID 2000b).

Partition Coefficient

The Log octanol/water partition coefficient for the acid was reported to be very low at 0.25-0.33, but was not evaluated for the Ca dipropionate salt, which is not a pure substance (IUCLID 2000b).

Water Solubility

Ca dipropionate was reported to have a substantial solubility of 260g/L at 20^{o}C (IUCLID 2000a) and the acid has a reported water solubility of 55.8 g/100ml @100^{o}C (HSDB 2002).

Environmental Fate and Transport

Available environmental fate and transport data for Ca dipropionate and propionic acid are shown in Table I and summarized below.

Photolysis

Photolysis was not measured for Ca dipropionate, but was measured for the free acid. The rate of degradation was 1.22-1.60 E^{-12} CM^3/mole/s @298^oK (Adkinson 1993).

Dissociation in water

One key characteristic of any metal carboxylate is that they readily dissociate from an ion pair into free metal and free acid as the pH is decreased. The equilibrium constants from a recent GLP dissociation study with Ca dipropionate can be seen in Table 2 (below), and the pKb values for propionate from the scientific literature are very consistent with the measured pKb2 value from the dissociation study (see bolded values).

Table 2 Comparison of pK values for Ca dipropionate, the metal carboxylate salt, and respective carboxylic acid[a]

Chemical Tested	Equilibrium Constants	
	pKb1	pKb2
Propionate	**4.87**	
Ca dipropionate	6.67	**4.75**

[a] See Table I and the Robust Summaries for additional details.

Biodegradation

The calcium salt of propionic acid is readily biodegradable and, as is the case for the acid, does not persist for long periods in water. The salt is 100% degraded after 7 days (Lezotte 2003) and the acid shows a similar rate of degradation of 95% in 10 days (IUCLID 2000b).

Monitoring data

Residues in foods, measured as propionic acid range from approximately 1100 to 2000 ppm (IUCLID 2000b, FASEB 1979).

Transport data

The Fugacity Level III analysis (Episuite v. 3.20) has been run for the Ca dipropionate (salt) and for the propionic acid dissociation product. This data is provided in the robust summaries. The propionic acid data is included in the

remarks section of 3.3.1 Transport (Fugacity). This modeling is not appropriate for either the salt or the acid due to the presence of the metal and ionized nature of the acid and the results must be carefully interpreted. The model is designed for neutral organics.

For the Ca dipropionate salt the fugacity calculations are performed assuming equal inputs to each compartment (air, water soil and sediment). Input parameters are generated within the Episuite program. Results show that the mass amount in each of four compartments partitions most strongly to soil and then water with only minor amounts in air and sediments (see Table below). Half-lives in these compartments are short ranging from 281 to 720 hr. with a longer half-life in sediment.

Ca dipropionate

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.0336	281	1000
Water	38.8	360	1000
Soil	61.1	720	1000
Sediment	0.0713	3.24e+003	0

Fugacity III modeling with acid propionate was specifically requested by the EPA and is presented under the remarks section for section 3.3.1 of the robust summary. The results are very similar to the salt with similar mass amounts in each compartment. The exception is the acid in the air compartment which has a larger mass amount than the Ca salt. The half-lives are shorter in three compartments and similar in sediments relative to Ca propionate. Half-lives range from 210 to 416 hr. for air water and soil. Sediments are slower, but have very little mass of propionic acid present.

Propionic acid

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	6.12	210	1000
Water	37.5	208	1000
Soil	56.3	416	1000
Sediment	0.0662	1.87e+003	0

Half-lives are short (<30 days) for air, water and soil for both Ca dipropionate and shorter (<18 days) for propionic acid indicating these materials would not result in any environmental persistence.

Ecotoxicity

Fish Toxicity

The calcium salt of propionic acid is practically non-toxic toward aquatic organisms with the reported 96-h LC50 value for *Leuciscus idus* reported as >10,000 mg/L (Table I) (BASF AG 1990). Toxicity of Ca dipropionate is less than the toxicity for the acid alone. The reported 96-h LC50s for the acid range from 67.1 to 86.3 mg/L for salmon and trout, respectively (IUCLID 2000b).

Invertebrate toxicity

The calcium salt of propionic acid is practically non-toxic toward aquatic organisms with reported 48-h LC50 value of > 500 mg/L (Table I) for *Daphnia* (BASF AG 1988). Toxicity of Ca dipropionate is less than the toxicity for the acid alone. The reported 96-h LC50s for the acid range from 67.1 to 86.3 mg/L for *Daphnia sp*., respectively (IUCLID 2000b).

Algal toxicity

The calcium salt of propionic acid is practically non-toxic toward algal species with reported 96-h IC50 value of > 500 mg/L (Table I) for *Scenedesmus subspecatus* (BASF AG 1988). Toxicity of Ca dipropionate is less than the toxicity for the acid alone. The reported 96-h LC50s for the acid range from 43.0 to 45.8 mg/L for *Scenedesmus subspecatus* (IUCLID 2000b).

Propionic acid is slightly toxicity to fish, invertebrates and algae with LC50 values ranging from 22.7 to 85.3 mg/L. The higher toxicity of the acid appears to be mainly due to the effects of low pH, as toxicity is greatly reduced under neutralized conditions.

Human Health Effects

Propionic acid is a normal intermediary metabolite in animals and humans. There is an extensive mammalian toxicity database available for this compound and the salt, Ca dipropionate.

Acute Mammalian Toxicity

Acute toxicity data is available Ca dipropionate for five of five acute endpoints (i.e., oral toxicity, inhalation, dermal toxicity, skin irritation and eye irritation) and two endpoints for the acid as presented and referenced in Table I (Kobayashi et al. 1976, BASF AG 1980, Patty Ind. Hyg. Toxicol. 1982, Symth et al. 1962, BASF AG 1979). Ca dipropionate shows a low order of acute toxicity and no irritation. The same order of toxicity is reported for propionate.

The acid has a low acute toxicity in animal studies (Table I), and is not reported to be corrosive or irritating to skin and eyes. Oral, inhalation and dermal LD50 or LC50 values are 3920-4380 mg/kg (rat), >5.6 mg/L (4 hrs., rat), and 500 mg/kg bw (rabbit). Reported acute toxicity in the rat exposed to propionic acid range from 2600 to 4290 mg/kg and >4.9 mg/L (4 hrs.) for oral and inhalation routes, respectively (IUCLID 2000b). Ca dipropionate is reported to be "not irritating", to either the skin or eye in rabbits using the Draize test (BASF AG 1979).

Genetic Toxicology - Mutation Assays

Neither Ca dipropionate nor propionic acid is mutagenic in *in vitro* Ames Tests. Genetic Toxicity Studies are available for Ca dipropionate and the carboxylic acid, propionate. *In vitro* Ames bacterial assays have been used to evaluate Ca dipropionate, including at least 11 strains with and without activation and with standard strains (e.g., TA 98, TA100, TA1535, TA1537, and TA1538) being evaluated in multiple studies (Altman et al. 1988a, Ohta et al. 1980, Litton Bionetics, Inc. 1974, Ishidata et al. 1984). All studies were negative for mutagenicity of Ca dipropionate. Similar *in vitro* studies with propionic acid and Na propionate were all negative. Similar results were observed in an *in vitro* study with Chinese hamster lung cells (without activation) and in sister chromatid exchange assays, using V79 cells (with and without activation) (Basler et al. 1987).

Genetic Toxicology – Clastogenic

Ca dipropionate is negative in cytogenetic or dominant lethal assays (Table I). Propionic acid is negative in a micronucleus test. In *in vivo* studies, Ca dipropionate showed no chromosomal aberrations in rat bone marrow cells and no dominant lethal mutations were observed (Litton Bionetics 1974). In the mouse exposure to Ca dipropionate resulted in increased reversion frequency, in one of three strains, but this was not dose-related. Propionic acid is reported to be negative in a micronucleus test (Basler et al. 1987).

In summary, all genetic toxicity studies using bacterial and mammalian cells, *in vitro* or *in vivo* are consistently negative.

Repeated Dose

There is extensive toxicity data for Ca dipropionate including several long-term repeated dose studies. This salt has a low order toxicity and it is typically less toxic that the acid alone, likely due to its lower acidity.

Repeated dose studies were conducted in rats and dogs with study periods ranging from 4 weeks to 90 days and exposure levels ranging up to 3320 mg/kg/day. No abnormalities in clinical or hematological examinations were observed. These changes were largely reversible. Changes in the fore stomach (e.g., hyperkeritosis and hyperplasia) were observed. These

changes were observed to occur equally with Ca and Na propionate, but were more marked with exposure to propionic acid. The changes were largely reversible, attributed to the acidity of the compound, and were not related to any systemic toxicity of the compound. Studies with Na propionate and propionic acid are also available. Some of these were conducted in parallel with Ca dipropionate (Altman et al. 1988a, Altman et al. 1988b, Harshbarger 1942).

Developmental Studies

Developmental studies have been conducted with five species (mouse, rabbit, hamster, rat, and chicken) (Food and Drug Research Labs Inc. 1972, Miss. State Univ. 1973). All five studies are rated as "Reliable with Restriction". In the four studies with mammalian species, no clearly substance-related effects on pregnancy parameters or on maternal or fetal survival were observed. The number of abnormalities in the treated groups was not different from negative controls. Parameters monitored including food and water consumption; body weight during early gestation; numbers of corpora lutea, implantation sites, resorption sites, and live and dead fetuses; body weights of live pups; dam urogenital tract examination; examination of all fetuses for gross abnormalities and one third for visceral abnormalities; and one third of fetuses were preserved, stained and examined for skeletal defects. In the study with chickens, Ca dipropionate was not teratogenic to developing chicken embryo at levels up to 100 mg/kg of egg pre-incubation or at 96 hours via the yolk and air cell. A dose of 10 mg/kg of egg produced high mortality rates compared to solvent controls, and a dose of 5 mg/kg administered pre-incubation via the yolk caused a high mortality rate (FASEB 1979).

Reproduction Studies

No Reproduction studies have been conducted with Ca dipropionate. Based on the results of repeated dose and developmental studies, the lack of accumulation from diet, and nearly ubiquitous exposure to propionate, no reproduction data is recommended.

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Table I: Summary of existing data for Ca dipropionate and its carboxylic acid

SIDS ENDPOINT	TEST/SPECIES	REPORTED VALUES Ca Dipropionate	Propionate[a]
Physicochemical Properties			
Melting Point		NA[1]	22.4°C
Boiling Point		….[b]	140.7–141.6 °C
Density		400 mg/m^3 [c]	
Vapor pressure		NA	5 hPa at 20 °C
Log Partition Coefficient		….[2]	0.25-0.33
Water Solubility		260 g/L at 20°C[c]--	49 g/100 ml at 0°C; 55.8 g/100 ml at 100°C[d]
Environmental Fate Parameters			
Photodegradation		--	1.22-1.60 E^{-12} cm^3/mol/s at 298°K[e]
Dissociation in water		pKb 6.7 and 4.75 at 20°C[f]	pKb 4.78
Monitoring Data	Food[3]		Ca 1100 to 2000 ppm[c,g]
Transport	NA[c]	See robust summary	See robust summary
Biodegradation		100% degraded after 7 days [h]	40% removal after 24 hrs. and 95% removal after 10 days.
Ecotoxicity			
Fish toxicity (96-h)	Bluegill Trout	>10,000 mg/L[i] (*Leuciscus idus)*	96-h LC50 for trout and salmon are 85.3 and 67.1 mg/L respectively
Invertebrate toxicity (48-h)	*Daphnia*	> 500 mg/L in (*Daphnia)*[j]	Ranged from 22.7 to 50 mg/L (*Daphnia)*
Algae toxicity (96-h)		>500 mg/L (Scenedesmus subspicatus)[j]	43 to 45.8 mg/L (Scenedesmus subspicatus)
Human Health Effects			
Acute	Oral LD50, rat	3920-4380 mg/kg bw[k]	3470, 4290, and 2600 mg/kg bw
	Inhalation LC50, rat	>5.6 mg/L (4 hrs.)[l]	>4.9 mg/L (4 hrs.)
	Dermal LD50, rabbit	500 mg/kg bw[m,n]	---
	Skin irritation, rabbit	Not irritating in Draize Test[o]	---
	Eye irritation	Not irritating[o]	---

SIDS ENDPOINT	TEST/SPECIES	REPORTED VALUES Ca Dipropionate	Propionate
Repeated dose	90-day oral	Reversible changes in stomach mucosa, but no mortality, no abnormalities following clinical and hematological examination and no change in organ weights were observed following exposures up to 3320 mg/kg/day[pqr]	pH related lesions in mucosal wall following 21 to 28 day exposures at 3320 mg/kg/day
Genetic Toxicology – mutation assay	Ames bacterial reversion assay	Negative[p,s,t,u]	Negative[v]
Genetic Toxicology – Clastogenic	Cytogenetic and dominant lethal assay	Negative (No increased chromosomal aberrations in bone marrow cells)[t]	Negative (micronucleus test)[v]
Reproductive		NA	NA
Developmental		No teratogenic effects in five species tested[x,y]	NA

[a] IUCLID 2000b; [b] RCC 2003; [c] IUCLID. 2000a; [d] HSDB. 2002; [e] Adkinson. 1993; [f] Lezotte 2003; [g] FASEB 1979; [h] BASF AG 1989b; [i] BASF AG 1990; [j] BASF AG 1988; [k] Kobayashi et al. 1976; [l] BASF AG 1980; [m] Patty Ind. Hyg. Toxicol. 1982; n Symth et al. 1962; [o] BASF AG 1979; [p] Altman et al. 1988a, [q] Altman et al. 1988b; [r] Harshbarger 1942; [s] Ohta et al. 1980; [t] Litton Bionetics, Inc. 1974; [u] Ishidata et al. 1984; [v] Basler et al. 1987; [x] Food and Drug Research Labs 1972; [y] Mississippi State University (1973).

1. Boiling Point could not be measured under conditions of GLP Test

2 The octanol/water partition coefficient was not measured for any of the metal carboxylates because they are salts which dissociate into ionized substances and they are not pure substances.

3 Estimated levels reported to be found in baked goods.

TEST PLAN AND RATIONALE FOR CA DIPROPIONATE

Propionic Acid, Calcium Salt	CASRN 4075-81-4

The Test Plan for Ca dipropionate is presented in Table II with supporting data for the carboxylic acid, propionate. The rationale for the Test Plan is based upon existing data as summarized above and in Table I. Some data is older, but this entire dataset has consistently served as an adequate basis for addressing food safety concerns by FDA, WHO, and most recently by the EPA (Office of Pesticide Programs). Furthermore, key studies have a rating of [1] reliable without restriction or [2] reliable with restrictions.

Physicochemical Properties

Data is available for all five SIDS endpoints listed in Tables I and II for either Ca dipropionate or propionic acid. The melting point and vapor pressure studies were considered not applicable and data was available for the free acid. A GLP boiling point study (OECD 103) was conducted, but the BP could not be determined under the conditions of the test (RCC 2003). The rationale for not conducting an octanol/water partition coefficient study with Ca dipropionate is based on the impurity of the compound (i.e. a salt), and an ionizeable substance. Using a compound with these characteristics to measure the partition coefficient is inappropriate. This would yield erroneous data. Data is available for the acid, which shows the Log Kow to be very low. No additional testing is recommended for any of the physicochemical endpoints.

Environmental Fate Parameters

Adequate data is available for three SIDS endpoints (i.e., photodegradation, dissociation and biodegradation) for Ca dipropionate and/or propionic acid. Data for transport in the environment is not provided and is not considered necessary. Standard models used for estimating transport do not accurately predict salts or ionized substances. Adequate biodegradation data are currently available for propionic acid component of the salt. The acid rapidly biodegrades (IUCLID 2000b). Further, aerobic degradation data already exists for Ca dipropionate and shows that it rapidly biodegrades. Because propionic acid is known to occur naturally and to readily be metabolized and degraded *in vivo,* and in the environment, estimating the environmental transport is considered unnecessary.

Ecotoxicity

Sufficient data is available for Ca dipropionate and for the carboxylic acid, propionic acid, for all three types of organisms (i.e., fish, invertebrates and algae). Based on the low order of toxicity for both the Ca salt and the acid for all three endpoints no additional studies are recommended.

Human Health Effects

Acute toxicity studies

Acute oral toxicity data is available for the Ca dipropionate and dissociation product propionic acid for five acute toxicity endpoints (oral toxicity, inhalation, dermal toxicity and skin and eye irritation) (Table I). No additional studies are recommended for acute toxicity endpoints.

Genotoxicity studies

Existing data for Ca dipropionate and the carboxylic acid, propionate are all negative (Table I). No additional genetic toxicity studies are proposed.

Higher tiered studies

Numerous repeated dose studies with Ca dipropionate, Na propionate, and the free acid, propionate, show a consistent lack of effects with the exception of changes in the digestive tract mucosa. These changes are largely reversible and attributed to generic pH effects and not to systemic toxicity. No additional repeated dose studies are recommended.

Developmental studies were conducted with four mammalian species and consistently showed a lack of teratogenic effects. There were no clearly substance-related effects on pregnancy parameters or on maternal or fetal survival. A study with chickens also showed a lack of teratogenicity. These studies were conducted in the early 1970's by the Food and Drug Research Labs and Litton Bionetics prior to the establishment of guidelines. They are rated as [2] Reliable with Restrictions. No additional studies are recommended.

No Reproduction studies have been conducted with Ca dipropionate. Based on the results of repeated dose and developmental studies, the lack of accumulation from diet, and nearly ubiquitous exposure of organisms to propionate via diet, no additional testing is recommended.

Table II: Test Plan Matrix: Ca dipropionate

	Information available	Ca Dipropionate	Propionate	GLP Study	Acceptable	Testing recommended
PHYSICOCHEMICAL PROPERTIES						
Melting Point	Y	Y	N	Y	Y	N
Boiling Point	Y	Y	Y	Y	Y	N
Vapor pressure	Y	N	Y	N	Y	N
Partition Coefficient	Y	N	Y	Y	Y	N
Water Solubility	Y	Y	N	N	N	N
ENVIRONMENTAL FATE PARAMETERS						
Photodegradation	Y	N	Y	--[C]	--	N
Dissociation in water	Y	Y	N	Y	Y	N
Transport	Y	Y	Y	N	Y	N
Biodegradation	Y	Y	Y	--	Y	N
ECOTOXICITY						
Fish toxicity (96-h)	Y	Y	Y	Y	Y	N
Invertebrate toxicity (48-h	Y	Y	Y	Y	Y	N
Algae toxicity (72-h)	Y	Y	Y	--	N	N
HUMAN HEALTH EFFECTS						
Acute						
Oral LD50, rat	Y	Y	Y	N	Y	N
Inhalation LC50, rat	Y	Y	Y	N	Y	N
Dermal LD50, rat	Y	Y	N	N	Y	N
Skin Irritation	Y	Y	N	N	Y	N
Eye Irritation	Y	Y	N	N	Y	N
Repeated dose	Y	Y	Y	Y	Y	N
Genetic Toxicology – mutation assay	Y	Y	Y	Y	Y	N
Genetic Toxicology – chromosomal aberration	Y	Y	Y	Y	Y	N
Reproductive	N	N	N	N	Y	N
Developmental	Y	Y	N	Y	Y	N

[A] U = undetermined
[B] Study currently being conducted
[c] -- means not applicable

1. General Information

Id 4075-81-4
Date December 20, 2002

201-16574C

Note: Appendix I refers to the IUCLID profile for Propionic acid

1.0 SUBSTANCE INFORMATION

Generic Name	:	Propionic acid, calcium salt
Chemical Name	:	Propionic acid, calcium salt
CAS Registry No.	:	4075-81-4
Component Cas Nos.	:	
EINECS No.	:	223-795-8
Structural Formula	:	$C_6H_{10}CaO_4$
Molecular Weight	:	186.2226
Synonyms and Tradenames	:	Calcium dipropionate; calcium propionate; calcium propanoate; propanoic acid, calcium salt; Bioban-C; Luprosil Spezial; Mycoban
Reference	:	http://www.chemfinder.com; MSDS dated 6/6/01 prepared by Kemin Industries, Ltd.; MSDS as cited in IUCLID (2000). IUCLID Dataset. European Chemicals Bureau, European Commission. Dataset for Calcium Dipropionate, 2/18/2000. [Subsequently referenced as IUCLID (2000)]

2.1 MELTING POINT

Type	:	
Guideline/method	:	OECD 103
Value	:	Could not be determined under the test conditions
Decomposition	:	
Sublimation	:	
Year	:	2003
GLP	:	yes
Test substance	:	Propionic acid, calcium salt
Method	:	Thermal Analysis and Capillary Test
Method detail	:	Thermal analysis was conducted using a Differential Scanning Calorimeter using a range of 25°C to 400°C with a change of 20 K/min. The capillary test was conducted using a Buechi Melting Point Tester, B-545. Samples were heated over a range of 25°C to 400°C
Remark	:	**Supporting data for dissocation products:** **Acid:** Melting point for propionic acid is reported to be 22.4°C (See Appendix I: 2.1)
Result	:	During Thermal Analysis endothermic peaks were observed starting at 90°C, a second, small peak at 260°C, and third peak at 360°C the remaining brown residue at the end of the study was half melted. In the Capillary Test the material was unchanged up to 360°C, but above 360°C the material began to sweat and at about 390°C the material started to melt and the color changed to a brown-grey.
Reliability	:	[1] Recent GLP Guideline Study
Reference	:	

2.2 BOILING POINT

Type	:	
Guideline/method	:	
Value	:	Not applicable.
Decomposition	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	**Supporting data for dissocation products:** **Acid:** Boiling point for propionic acid is reported to be 140.7 – 141.6°C (See Appendix I: 2.2)
Remark	:	
Reliability	:	
Reference	:	MSDS dated 6/4/01, prepared by Kemin Industries, Inc.

2.3 DENSITY

Type	:	Bulk density
Guideline/method	:	
Value	:	ca. 400 kg/m^3 at °C
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	

Result	:	
Remark	:	**Supporting data for dissocation products:** **Acid:** Density for propionic acid is reported to be 0.992 g/cm^3 at 20°C (See Appendix I: 2.3)
Reliability	:	[4] Not assignable. Only secondary reference
Reference	:	MSDS as cited in IUCLID (2000)

2.4 VAPOR PRESSURE

Type	:	
Guideline/method	:	
Value	:	Not applicable
Decomposition	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissocation products:** **Acid:** Vapor pressure for propionic acid reported to be 5 hPa at 20°C (See Appendix I: 2.4)
Reliability	:	
Reference	:	MSDS dated 6/4/01, prepared by Kemin Industries, Inc.

2.5 PARTITION COEFFICIENT

Type	:	
Guideline/method	:	
Partition coefficient	:	
Log Pow	:	at °C
pH value	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissocation products:** **Acid:** Log Pow for propionic acid reported to be 0.25 – 0.33 (See Appendix I: 2.5)
Reliability	:	
Reference	:	

2.6.1 SOLUBILITY IN WATER

Type	:	
Guideline/method		
Value	:	260 g/L at 20°C
pH value	:	9.2
concentration	:	200 g/L at 20 °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at °C
Description	:	

Stable	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	Other reported values: 49 g/100 mL at 0°C; 55.8 g/100 mL at 100°C (Hazardous Substances Data Bank, online at http://toxnet.nlm.nih.gov;) [Subequently referred to as HSDB, 2002]
Reliability	:	[4] Not assignable. Only secondary literature
Reference	:	MSDS as cited in IUCLID (2000)

2.7 FLASH POINT

Type	:	
Guideline/method	:	
Value	:	Not applicable
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissocation products:** **Acid:** Flash point for propionic acid reported to be 52.3°C (See Appendix I: 2.7)
Reliability	:	
Reference	:	MSDS, Fisher Scientific (2002) from http://www.fishersci.ca/msds/nsf

3.1.1 PHOTODEGRADATION

Type	:	
Guideline/method	:	
Light source	:	
Light spectrum	:	
Relative intensity	:	based on
Spectrum of substance	:	lambda (max, >295nm) epsilon (max) epsilon (295)
Conc. of substance	:	at °C
DIRECT PHOTOLYSIS		
Halflife (t1/2)	:	
Degradation	:	% after
Quantum yield	:	
INDIRECT PHOTOLYSIS		
Sensitizer	:	
Conc. of sensitizer	:	
Rate constant	:	
Degradation	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	1.22 - 1.60 E-12 cm^3/mol/s at 298ºK (measured for free acid)
Remark	:	**Supporting data for dissocation products:** **Acid:** The calculated time to 50% degradation by indirect photolysis of propionic acid was 4.7 years at room temperature and a pH of 9 with a rate constant of 0.47 x 10^9 L/mol.sec (See Appendix I: 3.1.1)
Reliability	:	[4] Not assignable. Only secondary literature
Reference	:	Atkinson, R., J. Phys. Chem. RefData, Mongraph 1; Meylan, W. and P. Howard, 1993, Atmospheric Oxidation Program Ver. 1.5, Syracuse Research Corp., NY; As cited in IUCLID (2000)

3.1.2 DISSOCIATION

Type	:	Dissociation constant determination
Guideline/method	:	OECD 112
pKb	:	6.76 and 4.75 at 20°C
Year	:	2002
GLP	:	Yes
Test substance	:	Calcium propionate (3445-1), lot number 05322JU, received from Aldrich Chemical Company. White powder, purity of 21.2% calcium
Approximate water solubility	:	Greater than 10,000 mg/L as determined visually in preliminary study
Method	:	OECD Guideline 112, Dissociation Constants in Water

Method detail	:	Three replicate samples of calcium propionate were prepared at a nominal concentration of 0.01 moles/L by dissolving 0.186 grams of test substance in 100 mL of degassed water (ASTM Type II). Each sample was titrated against 0.1 N hydrochloric acid while maintained at a test temperature of 20±1°C. At least 4 incremental additions were made before the first equivalence point and at least 10 incremental additions were made before the second equivalence point. The titration was carried past the final equivalence point. Values of pK were calculated for a minimum of 4 points on the titration curve. Phosphoric acid and 4-nitrophenol were used as reference substances.
Result	:	Mean (N = 3) pKb values were 6.76 (SD = 0.0488) and 4.75 (SD= 0.00808) at 20°C
Remark	:	The results indicate that dissociation of the test substance will occur at environmentally-relevant pH values (approximately neutral) and at physiologically-relevant pH values (approximately 1.2).
Reliability	:	[1] Reliable without restriction.
Reference	:	Lezotte, F.J. and W.B. Nixon, 2002. Determination of the dissociation constant of proprionic acid, calcium salt, Wildlife International, Ltd. Study No. 534C-120, conducted for the Metal Carboxylates Coalition.

3.2.1 MONITORING DATA

Type of measurement	:	
Media	:	Food
Concentration	:	ca. 2000 mg/l
Substance measured	:	
Method	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	Propionic acid, calcium salt is widely used as a mold and rope inhibitor in bread and bakery products at levels approx. 2000 ppm. Also used to prevent mold in certain cheeses and on certain fruit and vegetable products. (IUCLID, 2000). Weighted mean concentration added to baked goods 1100 ppm (FASEB, 1979)
Reliability	:	[1] Reliable without restriction
Reference	:	IUCLID (2000); Federation of American Societies for Experimental Biology (FASEB), Evaluation of the health aspects of propionic acid, calcium propionate, sodium propionate, dilauryl thiodipropionate, and thiodipropionic acid as food ingredients, Report of Select Committee on GRAS substances, prepared for US Food and Drug Administration, 1979. PB80104599 [Subequently referred to as FASEB, 1979]

Additional information: According to the Joint FAO/WHO Expert Committee on Food Additives, the estimate of the acceptable daily intakes for man are given as 0 – 10 mg/kg body weight (unconditional acceptance) and 10 – 20 mg/kg body weight (conditional acceptance). This is calculated as the sum of propionic acid, calcium propionate and sodium propionate. The Expert Commitee stated that there is no reason to believe that propionic acid differs toxicologically from its calcium and sodium salts. (FAO Nutrition Meetings, Report Series No. 40A,B,C, WHO/Food Add./67.29, Toxicological Evaluation of Some Antimicrobials, Antioxidants, Emulsifiers, Stabilizers, Flour-Treatment Agents, Acids and Bases.)

3.3.1 TRANSPORT (Fugacity)

Type	:	

Media : Air – sediment(s) – soil - water
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Year :
Test substance :
Method : EPISuite, v. 3.20
Method detail : Fugacity calculations performed assuming equal inputs to air, water and soil. Input parameters for physical/chemical properties calculated within EPISuite.
Result : Level III Fugacity Model (Full-Output):

==========

Chem Name : CALCIUM PROPIONATE
Molecular Wt: 186.22
Henry's LC : 1.43e-009 atm-m3/mole (calc VP/Wsol)
Vapor Press : 0.000652 mm Hg (Mpbpwin program)
Liquid VP : 0.00123 mm Hg (super-cooled)
Melting Pt : 53 deg C (Mpbpwin program)
Log Kow : -0.4 (Kowwin program)
Soil Koc : 0.163 (calc by model)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.0336	281	1000
Water	38.8	360	1000
Soil	61.1	720	1000
Sediment	0.0713	3.24e+003	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	7.65e-013	1.44	5.83	0.0479	0.194
Water	2.59e-014	1.3e+003	674	43.3	22.5
Soil	1.49e-012	1.02e+003	0	34	0
Sediment	2.37e-014	0.265	0.0248	0.00882	0.000825

Persistence Time: 579 hr
Reaction Time: 748 hr
Advection Time: 2.55e+003 hr
Percent Reacted: 77.3
Percent Advected: 22.7

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
Air: 281
Water: 360
Soil: 720
Sediment: 3240
Biowin estimate: 2.788 (weeks)

Advection Times (hr):
Air: 100
Water: 1000
Sediment: 5e+004

Note: results were unchanged when water solubility input was changed

from default to the reported value of 260 g/L.

Remark : **Supporting data for dissociation products:**
Acid: For propionic acid,

Fugacity Level III modeling for propionic acid.

Air – sediment(s) – soil - water
% (Fugacity Model Level I)
% (Fugacity Model Level I)
% (Fugacity Model Level I)
% (Fugacity Model Level II/III)
% (Fugacity Model Level II/III)

EPISuite, v. 3.20
Fugacity calculations performed assuming equal inputs to air, water and soil. Input parameters for physical/chemical properties calculated within EPISuite.

Level III Fugacity Model (Full-Output):
==========

Chem Name : Propanoic acid
Molecular Wt: 74.08
Henry's LC : 4.45e-007 atm-m3/mole (Henry database)
Vapor Press : 6.04 mm Hg (Mpbpwin program)
Log Kow : 0.33 (Kowwin program)
Soil Koc : 0.877 (calc by model)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	6.12	210	1000
Water	37.5	208	1000
Soil	56.3	416	1000
Sediment	0.0662	1.87e+003	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	1.79e-010	179	544	5.97	18.1
Water	1e-011	1.11e+003	334	37	11.1
Soil	5.19e-010	832	0	27.7	0
Sediment	8.65e-012	0.218	0.0118	0.00726	0.000392

Persistence Time: 296 hr
Reaction Time: 419 hr
Advection Time: 1.01e+003 hr
Percent Reacted: 70.7
Percent Advected: 29.3

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
Air: 210.4
Water: 208.1
Soil: 416.2
Sediment: 1873
Biowin estimate: 3.400 (days-weeks)

Reliability : (1) valid with restrictions; calculated using scientifically acceptable method,

although the applicability of the Fugacity model to test substances such as carboxylic acids is uncertain.

Reference :

3.5 BIODEGRADATION

Type	:	Aerobic
Guideline/method	:	OECD 302 B
Inoculum	:	Other: activated sludge
Concentration	:	300 mg/L related to DOC (dissolved organic carbon)
Contact time	:	
Degradation	:	100 % after 7 day(s)
Result	:	
Kinetic of test subst.	:	3 hours = 18 % (specify time and % degradation)
Control substance	:	
Kinetic	:	%
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	OECD Guideline 302B, Inherent biodegradability: Modified Zahn-Wellens Test
Method Detail	:	
Result	:	biodegradable
Remark	:	**Supporting data for dissociation products:** **Acid:** Propionic acid is biodegradable in activated sludge, with 40.4% removal of an initial concentration of 500 mg/L after 24 hours and 95% removal of an intial concentration of 400 mg/L after 10 days (See Appendix I: 3.5)
Reliability	:	[4] Not assignable. Only secondary literature
Reference	:	BASF AG, Labor Oekologie, unveroeffentlichte Untersuchung,(Laboratory of Ecology, unpublished research) (Ber. V.24.01.89. As cited in IUCLID (2000)

3.7 BIOCONCENTRATION

Type	:	
Guideline/method	:	
Species	:	
Exposure period	:	at °C
Concentration	:	
BCF	:	
Elimination	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

4.1 ACUTE TOXICITY TO FISH

Type	:	Static
Guideline/method	:	DIN38412 Teil 15, Bestimmung der Wirkkung von Wasserinhaltsstoffen auf Fische
Species	:	*Leuciscus idus*, freshwater fish
Exposure period	:	96 hours
NOEC	:	5000 mg/L
LC0	:	5000 mg/L
LC50	:	> 10000 mg/L
LC100	:	> 10000 mg/L
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	No
Year	:	1982
GLP	:	No
Test substance	:	Calcium dipropionate
Method	:	DIN38412 Teil 15, Bestimmung der Wirkkung von Wasserinhaltsstoffen auf Fische
Method detail	:	
Result	:	Lethality to 2 of 10 fish after 96 hours at 10000 mg/L, no lethality at 5000 mg/L. No toxic symptoms detectable.
Remark	:	For sodium propionate, the 24-h LC50 for *Lepomis macrochirus* was 5000 mg/L. **Supporting data for dissociation products:** **Acid:** For propionic acid, the 48-h LC50 for *Cyprinus carpio* was 72 mg/L and the 24-h LC50 for *Lepomis macrochirus* was 188 mg/L. (See Appendix I: 4.1) Reported 96-h LC50 values for propionic acid include 85.3 ppm (95% CI 73.0 – 99.7ppm) for *Lepomis macrochirus* and 67.1 ppm (95% CI: 61.6 – 73.2 ppm) for *Oncorhynchus mykiss*. (US EPA Office of Pesticide Programs Environmental Effects Database, cited in ECOTOX)
Reliability	:	[4] Not assignable. Only secondary literature
Reference	:	BASF AG, Dept. Toxicology, unpublished study 10F0958/885187, 08.01.1990. As cited in IUCLID (2000)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	Static
Guideline/method	:	Directive 84/449/EEC, C.2, “Acute toxicity for *Daphnia*“
Species	:	*Daphnia magna* (water flea)
Exposure period	:	48 hours
NOEC	:	
EC0	:	250 mg/L
EC50	:	> 500 mg/L
EC100	:	> 500 mg/L
Other	:	24 h EC50 = 250 mg/L
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	No
Year	:	1989
GLP	:	No
Test substance	:	Calcium dipropionate

Method	:	Directive 84/449/EEC, C.2, “Acute toxicity for *Daphnia*“
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** For propionic acid, the 48-h EC50 for *Daphnia magna* was reported to be 50 mg/L. (See Appendix I: 4.2). Reported 48-h EC50 value for *Daphnia magna* for propionic acid was 22.7 ppm (95% CI: 21.0 – 24.6 ppm) [US EPA Office of Pesticide Programs Environmental Effects Database, cited in ECOTOX].
Reliability	:	[4] Not assignable. Only secondary literature
Reference	:	BASF AG, Labor Oekologie, unveroeffentlichte Untersuchung,(Laboratory of Ecology, unpublished research) (1540/88). As cited in IUCLID (2000)

4.3 TOXICITY TO AQUATIC PLANTS (e.g., Algae)

Type	:	Growth inhibition
Guideline/method	:	OECD guideline 201, Algae, Growth Inhibition Test
Species	:	*Scenedesmus subspicatus* (freshwater green algae)
Endpoint	:	
Exposure period	:	72 hours
NOEC	:	
LOEC	:	
EC0	:	
EC10	:	
EC50	:	> 500 mg/L
EC20	:	> 500 mg/L
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	No
Year	:	1988
GLP	:	No
Test substance	:	Calcium dipropionate
Method	:	OECD guideline 201, Algae, Growth Inhibition Test
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** For propionic acid, the 72-h EC50 for *Scenedesmus subspicatus* was reported to be 43 - 45.8 mg/L (See Appendix I: 4.3)
Reliability	:	[4] Not assignable. Only secondary literature
Reference	:	BASF AG, Labor Oekologie, unveroeffentlichte Untersuchung,(Laboratory of Ecology, unpublished research) (1540/88). As cited in IUCLID (2000)

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In vitro/in vivo	:	
Type	:	
Guideline/method	:	
Species	:	
Number of animals	:	
Males	:	
Females	:	
Doses	:	
Males	:	
Females	:	
Vehicle	:	
Route of administration	:	
Exposure time	:	
Product type guidance	:	
Decision on results on acute tox. tests	:	
Adverse effects on prolonged exposure	:	
Half-lives	:	1st.: 2nd.: 3rd.:
Toxic behavior	:	
Deg. product	:	
Deg products CAS#		
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Propionic acid is a normal intermediary metabolite in animals and humans. Propionic acid occurs naturally in various foods including butter and cheese. (FASEB, 1979).
Reliability	:	
Reference	:	

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Guideline/method	:	
Species	:	Rat
Strain	:	
Sex	:	Male and female
Number of animals	:	
Vehicle	:	
Doses	:	
LD50	:	3920 – 4380 mg/kg bw.
Year	:	
GLP	:	
Test substance	:	Calcium dipropionate
Method	:	
Method detail	:	
Result	:	LD50 was 3920 – 4380 mg/kg bw. For male rats, LD50 was 4280 or 4380 mg/kg. For female rats, LD50 was 3920 or 4040 mg/kg

Remark	:	For sodium propionate, the LD50 for the rat was 5100 mg/kg. **Supporting data for dissociation products:** **Acid:** For propionic acid, the following LC50 values for rats have been reported: 3470 mg/kg; 4290 mg/kg; 2600 mg/kg. For sodium propionate, the LD50 for the rat was 5100 mg/kg. (See Appendix I: 5.1.1)
Reliability	:	[4] Not assignable. Text is in Japanese, only tables appear in English
Reference	:	Kobayashi, H., H. Ichikawa, N. Kamiya, S. Yoshida, and K. Hiraga (1976). The results on acute toxicities of food additives. Ann. Rep. Tokyo Metr. Res. Lab. P.H., 27-2, 159-160. Also cited and interpreted in IUCLID (2000)
Additional references	:	Other oral LD50 values for rats: 5160 mg/kg bw; 2600 mg/kg bw; 6400 mg/kg bw (As cited in IUCLID, 2000)

Type	:	LD50
Guideline/method	:	
Species	:	Mouse
Strain	:	
Sex	:	Male and female
Number of animals	:	
Vehicle	:	
Doses	:	
LD50	:	2350 - 2900 mg/kg bw.
Year	:	
GLP	:	
Test substance	:	Calcium dipropionate
Method	:	
Method detail	:	
Result	:	LD50 was 2350 - 2900 mg/kg bw. For male mice, LD50 was 2350 or 2600 mg/kg. For female mice, LD50 was 2400 or 2900 mg/kg
Remark	:	For a similar compound, sodium propionate, the LD50 for the mouse was 5100 mg/kg bw, as cited in FASEB Report: Evaluation of the health aspects of propionic acid..., prepared for FDA, 1979.
Reliability	:	[4] Not assignable. Text is in Japanese, only tables appear in English
Reference	:	Kobayashi, H., H. Ichikawa, N. Kamiya, S. Yoshida, and K. Hiraga (1976). The results on acute toxicities of food additives. Ann. Rep. Tokyo Metr. Res. Lab. P.H., 27-2, 159-160. Also cited and interpreted in IUCLID (2000)
Additional references		LD50 of 3340 mg/kg for DD-strain mice is cited in FASEB (1979)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	Limit test
Guideline/method	:	
Species	:	Rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Exposure time	:	4 hours
LC50	:	> 5.4 mg/L
Year	:	
GLP	:	No
Test substance	:	
Method	:	
Method detail	:	
Result	:	The LC50 was reported to be > 5.4 mg/L
Remark	:	Also tested sodium propionate, dust aerosol, with same result.

Supporting data for dissocation products:
Acid: Under similar conditions as reported above for calcium propionate and sodium propionate, the LC50 for propionic acid was >4.9 mg/L. (See Appendix I: 5.1.2)

Reliability : [4] Not assignable. Only secondary literature
Reference : BASF AG, Dept. Toxicology, unpublished study 78/29, 19.12.1980. As cited in IUCLID (2000)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Guideline/method	:	
Species	:	Rabbit
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
LD50	:	500 mg/kg bw
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	The LD50 was reported as 500 mg/kg bw
Remark	:	No further information. Same result cited for propionic acid
Reliability	:	[4] Not assignable. Only secondary literature.
Reference	:	Patty Ind. Hyg. Toxicol. (1982); Smyth, H.F. et al., Am. Ind. Hyg. Assoc. J. 23:95-107 (1962); Union Carbide Datasheet. As cited in IUCLID (2000)

5.2.1 SKIN IRRITATION

Type	:	Skin irritation
Guideline/method	:	
Species	:	Rabbit
Strain	:	
Sex	:	
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	
Vehicle	:	
Classification	:	
Year	:	1973
GLP	:	No
Test substance	:	Calcium propionate feed grade, sodium propionate
Method	:	Draize test
Method detail	:	
Result	:	Not irritating
Remark	:	Sodium propionate was found to be not irritating in the Draize skin irritation test with rabbits. (See Appendix 1: 5.2.2) **Supporting data for dissociation products:** **Acid:** Propionic acid caused mild irritation to rabbits following 4 h closed contact of the skin with a 2.5% aqueous solution, mild to moderate irritation with 25% solution, and moderate to severe irritation and corrosion at

		concentrations of 40% and above. Propionic acid ws a severe irritant to guinea pig skin. (See Appendix I: 5.2.1)
Reliability	:	[4] Not assignable. Only secondary literature
Reference	:	BASF AG, Dept. Toxicology, unpublished study 78/28, 78/29 and 78/30. 25.04.1979. As cited in IUCLID (2000)

5.2.2 EYE IRRITATION

Type	:	Eye irritation
Guideline/method	:	
Species	:	Rabbit
Strain	:	
Sex	:	
Concentration	:	
Dose	:	
Exposure time	:	
Number of animals	:	
Vehicle	:	
Classification	:	
Method	:	
Year	:	1973
GLP	:	
Test substance	:	Calcium propionate feed grade, sodium propionate
Method	:	Draize test
Method detail	:	
Result	:	Not irritating
Remark	:	Sodium propionate was found to be not irritating in the Draize eye irritation test with rabbits. Propionic acid was irritating to rabbits (See Appendix 1: 5.2.2)
Reliability	:	[4] Not assignable. Only secondary literature
Reference	:	BASF AG, Dept. Toxicology, unpublished study 78/28, 78/29 and 78/30. 25.04.1979. As cited in IUCLID (2000)

5.4 REPEATED DOSE TOXICITY

Type	:	Repeated dose
Guideline/method	:	
Species	:	Rat
Strain	:	Wistar Han/BGA
Sex	:	Male and female
Number of animals	:	40
Route of admin.	:	Oral feed
Exposure period	:	90 days
Frequency of treatment	:	Daily
Post exposure period	:	One group for control and two highest doses over 90 and 180 days
Doses	:	0.2, 0.5, 1 and 4% (= 166, 415, 830, 3320 mg/kg bw)
Control group	:	Yes
NOAEL	:	0.2% (166 mg/kg) for males, 1% (830 mg/kg) for females
LOAEL	:	
Other	:	
Year	:	
GLP	:	
Test substance	:	Not clarified but presumed to be calcium propionate
Method	:	

Method detail	:	
Result	:	No abnormalities in clinical and hematological examination and organ weights. In forestomach of males, hyperkeratosis and hyperplasia of mucosa, at 4% 1/10 atypical basal cell proliferation and 5/10 dysplasia. In forestomach of females, hyperkeratosis and hyperplasia at 4% (hyperkeratosis also in controls) in different regions of forestomach. Effects largely reversible during 90-day post exposure observation period. After 180 days appearance of first age-related changes in the forestomach.
Remark	:	Forty female Wistar rats fed sodium propionate at 20000 ppm (1320 mg/kg) for one year did not exhibit any hematological, clinicochemical, or urinalytic changes. There were no changes in organ weights and the body weight at the end of the study was 290 g versus 299 g in controls. [Imai, S. , S. Sekigawa, J. Morimoto, Y. Ohno, H. Yamamoto, T. Okuyama, K. Nakamor and Y. Tsubura (1981). Additive toxicity of sodium propionate and/or sorbic acid in SLC-Wistar rats for one year. J. Nara. Med. Ass. 32:715-722. Also interpreted and cited in IUCLID (2000)]. **Supporting data for dissociation products:** **Acid:** Beagles fed propionic acid for 90 days exhibited lack of appetite at the highest dose (2000 mg/kg bw) but no other clinical, hematological or clinico-chemical effects. (See Appendix I: 5.4). Propionic acid in the diet (4% or 3320 mg/kg) of rats caused enhanced incorporation of methyl-H3-thymidine in the mucosa of the forestomach after 21 and 28 days of treatment, and macroscopic and histological lesions (general and nodular mucosal thickening) were observed in the forestomach after 27 days. This may reflect the response of the forestomach epithelium to changed pH (Rodrigues, C., Lok, E., Nera, E., Iverson, F., Page, D., Karpinski, K. and Clayson, D.B., 1986. Short-term effects of various phenols and acids on the Fischer 344 male rat forestomach epithelium, Toxicology 38:103-117).
Reliability	:	[4] Not assignable. Only secondary literature
Reference	:	Altman H-J and Grunow, W., „Ergeb. Neuer. Fuetterungsvers.m.Propions.u.i.Salzen“ unpubl. Report Fed. Health Agency (BGA Berlin ,’88). As cited in IUCLID (2000)

5.5 GENETIC TOXICITY ‘IN VITRO‘

Type	:	Mutagenicity
Guideline/method	:	
System of testing	:	Repair test (rec assay) and reversion assay
Species	:	*Bacillus subtilis* (rec assay); *Escherichia coli* and *Salmonella typhimurium* (reversion assay)
Strain	:	*B. subtilis*: H17 Rec^+ and M45Rec^-; *E.coli*: WP2 *hcr trp*; *S. typhimurium*: TA98, TA100, TA1535, TA 1537, TA1538
Test concentrations	:	No data specified
Cytotoxic concentr.	:	
Metabolic activation	:	Conducted both with and without activation. Activation system consisted of S-9 mix prepared from liver homogenate of Arochlor 1254-pretreated male rats (i.p at 500 mg/kg)
Year	:	
GLP	:	No data
Test substance	:	Calcium propionate; purity > 98%
Method	:	Rec assay using paper disk method, according to Shirasu, Y. et al., Mutat. Res. 56: 121-129. Reverse mutation assay according to Ames, B.N., Mutat. Res. 31: 347-364
Method detail	:	REC-assay (repair test): Overnight cultures of *B. subtiis* H17 Rec^+ and M45$^-$ were streaked on to a B2 auger plate and a paper disk soaked with

0.02 ml of a solution of Ca propionate was placed on the starting part of the bacterial streaks. Plates were incubated for 1 to 2 days. The length of the inhibition zone for each streak was measured and differences of 3 mm were considered positive. Kanamycin was a positive control.
Reverse mutation assay: *Eschoricia coli* W2 her and 5 *Salmonella typhurium* testers strains were used in a top-auger overlay method. Ca propionate was dissolved in DMSO and, with and without addition of S9 fraction (from AROCHLOR 1254 exposed rats) in buffer. This soluton was poured on to minimal glucose agar plate with modified Vogel-Banner E medium. Revertants were scored after two days incubation at 37°C.

Result : Negative

Remark : Sodium propionate was negative in the Ames assay. (Ishidate, et al., 1984, as cited in Basler et al., 1987)
Supporting information for dissociation products:
Acid: Propionic acid was evaluated for genotoxic properties using the *E.coli* DNA repair assay, the SOS chromotest, the Salmonella/microsome mutagenicity test, the sister chromatid exchange test *in vitro* and the micronucleus test *in vivo*. All tests except the DNA repair assay yielded negative results. The authors concluded that this evidence supported other evidence, including studies with calcium and sodium propionate, that propionic acid was not mutagenic (Basler, A., von der Hude, W. and Scheutwinkel, M., 1987. Screening of the food additive propionic acid for genotoxic properties, Fd. Chem. Toxic. 25:287-290). The authors conclude that since calcium and sodium propionate dissociate in aqueous solution and react with a proton to form the acid, results with all three test substances can be compared.

Reliability : [2] Reliable with restrictions. Conducted according to scientifically acceptable methods.

Reference : Ohta, T., M. Moriya, Y. Kaneda, K. Watanabe, T. Miyazawa, F. Sugiyama and Y. Shirasu (1980). Mutagenicity screening of feed additives in the microbial system. Mutat. Res. 77: 21-30. Also cited in IUCLID (2000)

5.6 GENETIC TOXICITY 'IN VIVO'

Type : Cytogenetic assay and dominant lethal assay
Guideline/method :
Species : Rat
Strain : Sprague-Dawley CD
Sex : male
Route of admin. : Oral (gastric intubation)
Exposure period : Acute study: single dose, then observed for 10 days. Subacute study: Dosed every 24 hours for 5 days.
Doses : 5000 mg/kg (single dose) or 50, 500 and 5000 mg/kg (subacute)
Year : 1973
GLP : No
Test substance : Calcium dipropionate
Method :
Method detail : Negative control (saline) and postive control used. Single dose study conducted with two rats at 5000 mg/kg bw, then repeated with ten rats at same dose.
Result : No increase of chromosome aberrations in bone marrow cells. In addition, no dominant lethal mutations detected.
Remark : No increase in chromosome abberations in the bone marrow cells of the rat were observed after dosing with sodium propionate (See Appendix I: 5.6)
Supporting data for dissociation products:

Acid: Propionic acid was not genotoxic in the micronucleus test *in vivo*. (Basler, A., von der Hude, W. And Scheutwinkel, M., 1987. Screening of the food additive propionic acid for genotoxic properties, Fd. Chem. Toxic. 25:287-290).

Reliability	:	[1] Reliable without restrictions. Methods described and complete data presented. Comparable to guideline study.
Reference	:	Litton Bionetics, Inc. (1974). Mutagenic evaluation of compound FDA 71-36. Report prepared for FDA, NTIS PB 245448 (1974).

Type	:	Host mediated assay
Guideline/method		
Species	:	Mouse
Strain	:	ICR
Sex	:	Male
Route of admin.	:	Oral (gastric intubation)
Exposure period	:	Acute study: single dose, then observed for 10 days. Subacute study: Dosed every 24 hours for 5 days.
Doses	:	5000 mg/kg (single dose) or 50, 500 and 5000 mg/kg (subacute)
Year	:	1973
GLP	:	No
Test substance	:	Calcium dipropionate
Method	:	
Method detail	:	Negative control (saline) and positive controls used. Ten animals at each dose level for both acute and subacute study.
Result	:	Increase in reversion frequency of *S. typhimurium* G-46 but not dose-related. No mutations in strain TA-1530 and *Saccharomyces cerevisiae* D3. A single dose was marginally recombinogenic in the acute trials using *S. cerevisiae* D3 but none of the other acute or subacute doses showed this effect.
Remark	:	
Reliability	:	[1] Reliable without restrictions. Methods described and complete data presented. Comparable to guideline study.
Reference	:	Litton Bionetics, Inc. (1974). Mutagenic evaluation of compound FDA 71-36. Report prepared for FDA, NTIS PB 245448 (1974).

5.8.2 DEVELOPMENTAL TOXICITY

Type	:	Developmental toxicity
Guideline/method	:	
Species	:	Mouse
Strain	:	Albino CD-1
Sex	:	Female
Route of admin.	:	Gavage
Exposure period	:	Day 6 -15 of gestation
Frequency of treatment	:	Daily
Duration of test	:	Until day 17 of gestation
Doses	:	3, 14, 65, 300 mg/kg/d
Control group	:	Yes, concurrent sham-treated
NOAEL maternal tox.	:	NOAEL not reported, but no effects seen at highest dose (300 mg/kg/d)
NOAEL teratogen.	:	NOAEL not reported, but no effects seen at highest dose (300 mg/kg/d)
Other	:	
Other	:	
Other	:	
Year	:	1972
GLP	:	No

Test substance	:	Calcium propionate
Method	:	
Method detail	:	Groups of 25-30 mice were used. Negative controls were intubated with water, positive controls were administered 150 mg/kg/d of aspirin. Animals were observed daily for appearance, behavior, food and water consumption. Body weight was recorded on days 0,6,11,15 and 17 of gestation. On day 17 of gestation, all dams were subjected to Casarean section and the number of corpora lutea, implantation sites, resorption sites, and live and dead fetuses recorded. Body weights of live pups recorded and urogenital tract of each dam was examined for anatomical normality. All fetuses were examined grossly for abnormalities. One third of the fetuses of each litter underwent detailed visceral examination under 10x magnification; two thirds cleared, stained and examined for skeletal defects.
Result	:	No clearly substance-related effects on pregnancy parameters or on maternal or fetal survival were observed. The number of abnormalities in the soft or skeletal tissues in treated groups was not different from negative controls.
Remark	:	
Reliability	:	[2] Reliable with restrictions. Generally comparable to current guideline methodology, but level of recorded detail (both methods and results) is not consistent with current guidelines. No statistical analyses of results was performed.
Reference	:	Food and Drug Research Labs, Inc.,(1972) Teratologic Evaluation of FDA 71-36 (Calcium propionate) in mice, rats, hamsters and rabbits, Final report for FDA, NTIS PB-221778.

Type	:	Developmental toxicity
Guideline/method	:	
Species	:	Rabbit
Strain	:	Dutch-belted
Sex	:	Female
Route of admin.	:	Gavage
Exposure period	:	Day 6 -18 of gestation
Frequency of treatment	:	Daily
Duration of test	:	Until day 29 of gestation
Doses	:	4, 19, 86, 400 mg/kg/d
Control group	:	Yes, concurrent sham-treated
NOAEL maternal tox.	:	NOAEL not reported, but no effects seen at highest dose (400 mg/kg/d)
NOAEL teratogen.	:	NOAEL not reported, but no effects seen at highest dose (400 mg/kg/d)
Other	:	
Other	:	
Other	:	
Year	:	
GLP	:	No
Test substance	:	Calcium propionate
Method	:	
Method detail	:	Groups of 15-25 rabbits were used. Negative controls were intubated with water, positive controls were administered 2.5 mg/kg of 6-aminonicotinamide on day 9. Animals were observed daily for appearance, behavior, food and water consumption. Body weight was recorded on days 0,6,12,18 and 29 of gestation. On day 29 of gestation, all dams were subjected to Casarean section and the number of corpora lutea, mplantation sites, resorption sites, and live and dead fetuses recorded. Body weights of live pups recorded and urogenital tract of each dam was

		examined for anatomical normality. All fetuses were examined grossly for abnormalities. Live fetuses were placed in an incubator for 24 hours for the evaluation of neonatal survival. All surviving pups were sacrificed and examined for visceral abnormalities (by dissection), then cleared, stained and examined for skeletal defects.
Result	:	No clearly substance-related effects on pregnancy parameters or on maternal or fetal survival were observed. The number of abnormalities in the treated groups was not different from negative controls.
Remark	:	
Reliability	:	[2] Reliable with restrictions. Generally comparable to current guideline methodology, but level of recorded detail (both methods and results) is not consistent with current guidelines. No statistical analyses of results was performed.
Reference	:	Food and Drug Research Labs, Inc.,(1972) Teratologic Evaluation of FDA 71-36 (Calcium propionate) in mice, rats, hamsters and rabbits, Final report for FDA, NTIS PB-221778.
Type	:	Developmental toxicity
Guideline/method	:	
Species	:	Hamster
Strain	:	Golden hamsters from an outbred strain (no further data)
Sex	:	Female
Route of admin.	:	Gavage
Exposure period	:	Day 6 -10 of gestation
Frequency of treatment	:	Daily
Duration of test	:	Until day 14 of gestation
Doses	:	4, 19, 86, 400 mg/kg/d
Control group	:	Yes, concurrent sham-treated
NOAEL maternal tox.	:	NOAEL not reported, but no effects seen at highest dose (400 mg/kg/d)
NOAEL teratogen.	:	NOAEL not reported, but no effects seen at highest dose (400 mg/kg/d)
Other	:	
Other	:	
Other	:	
Year	:	
GLP	:	No
Test substance	:	Calcium propionate
Method	:	
Method detail	:	Groups of 22 golden hamsters were used. Negative controls were intubated with water, positive controls were administered 250 mg/kg/d of aspirin. Animals were observed daily for appearance, behavior, food and water consumption. Body weight was recorded on days 0,8,10, and 14 of gestation. On day 14 of gestation, all dams were subjected to Casarean section and the number of corpora lutea, implantation sites, resorption sites, and live and dead fetuses recorded. Body weights of live pups recorded and urogenital tract of each dam was examined for anatomical normality. All fetuses were examined grossly for abnormalities. One third of the fetuses of each litter underwent detailed visceral examination under 10x magnification; two thirds cleared, stained and examined for skeletal defects.
Result	:	No clearly substance-related effects on pregnancy parameters or on maternal or fetal survival were observed. The number of abnormalities in the treated groups was not different from negative controls.
Remark	:	
Reliability	:	[2] Reliable with restrictions. Generally comparable to current guideline methodology, but level of recorded detail (both methods and results) is not

		consistent with current guidelines. No statistical analyses of results was performed.
Reference	:	Food and Drug Research Labs, Inc.,(1972) Teratologic Evaluation of FDA 71-36 (Calcium propionate) in mice, rats, hamsters and rabbits, Final report for FDA, NTIS PB-221778.
Type	:	Developmental toxicity
Guideline/method	:	
Species	:	Rat
Strain	:	Albino, Wistar
Sex	:	Female
Route of admin.	:	Oral intubation
Exposure period	:	Day 6 -15 of gestation
Frequency of treatment	:	Daily
Duration of test	:	Until day 20 of gestation
Doses	:	3, 14, 65, 300 mg/kg/d
Control group	:	Yes, concurrent sham-treated
NOAEL maternal tox.	:	NOAEL not reported, but no effects seen at highest dose (300 mg/kg/d)
NOAEL teratogen.	:	NOAEL not reported, but no effects seen at highest dose (300 mg/kg/d)
Other	:	
Other	:	
Other	:	
Year	:	
GLP	:	No
Test substance	:	Calcium propionate
Method	:	
Method detail	:	Groups of 24 rats were used. Negative controls were intubated with water, positive controls were administered 250 mg/kg/d of aspirin. Animals were observed daily for appearance, behavior, food and water consumption. Body weight was recorded on days 0,6,11,15 and 20 of gestation. On day 20 of gestation, all dams were subjected to Casarean section and the number of corpora lutea, implantation sites, resorption sites, and live and dead fetuses recorded. Body weights of live pups recorded and urogenital tract of each dam was examined for anatomical normality. All fetuses were examined grossly for abnormalities. One third of the fetuses of each litter underwent detailed visceral examination under 10x magnification; two thirds cleared, stained and examined for skeletal defects.
Result	:	No clearly substance-related effect on pregnancy parameters or on maternal or fetal survival were observed. The number of abnormalities in the treated groups was not different from negative controls.
Remark	:	
Reliability	:	[2] Reliable with restrictions. Generally comparable to current guideline methodology, but level of recorded detail (both methods and results) is not consistent with current guidelines. No statistical analyses of results was performed.
Reference	:	Food and Drug Research Labs, Inc.,(1972) Teratologic Evaluation of FDA 71-36 (Calcium propionate) in mice, rats, hamsters and rabbits, Final report for FDA, NTIS PB-221778.
Type	:	Developmental toxicity
Guideline/method	:	
Species	:	Chicken
Strain	:	
Sex	:	
Route of admin.	:	Injection into air cell or yolk sac of eggs

Exposure period	:	Preincubation or at 96 hours
Frequency of treatment	:	
Duration of test	:	
Doses	:	5, 10, 100 mg/kg of egg
Control group	:	Yes, concurrent vehicle
NOAEL maternal tox.	:	
NOAEL teratogen.	:	100 mg/kg
Other	:	High mortality rates at doses of 5 and 10 mg/kg
Other	:	
Other	:	
Year	:	
GLP	:	
Test substance	:	Calcium propionate
Method	:	
Method detail	:	
Result	:	Not teratogenic to developing chicken embryo at levels up to 100 mg/kg of egg preincubation or at 96 h via the yolk and air cell. A dose of 10 mg/kg of egg produced high mortality rates compared to solvent controls, and a dose of 5 mg/kg administered preincubation via the yolk caused a high mortality rate.
Remark	:	
Reliability	:	[4] Not assignable. Only secondary reference.
Reference	:	Mississippi State University, 1973. Investigation of the toxic effects of GRAS substances to the developing chicken embryo: calcium propionate. As cited in FASEB (1979)

5.8.3 TOXICITY TO REPRODUCTION

Type	:	
Guideline/method	:	
In vitro/in vivo	:	
Species	:	
Strain	:	
Sex	:	
Route of admin.	:	
Exposure period	:	
Frequency of treatm.	:	
Duration of test	:	
Doses	:	
Control group	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

6.0 OTHER INFORMATION

6.1 CARCINOGENICITY

Supporting information for dissociation products:

Acid: Pre-neoplastic/pre-cancerous changes in rats fed 4% (2640 mg/kg) propionic acid were reported by Griem (1985). Hyperplasia, hyperplastic ulcers, papillomas and proliferation of the basal cells in the mucuosa of the forestomach were observed. Over the lifetime exposure, the high dose (4% propionic acid) resulted in 19/20 rats with dysplasia of glandular stomach mucosa while this effect was seen in 10/20 rats at the low dose (0.4%) and 5/20 control rats. However, Basler et al. (1987) concluded that propionic acid is not mutagenic and that genotoxic events are unlikely to be involved in the generation of these forestomach lesions. (See Appendix I: 5.7; also Basler, A., von der Hude, W. And Scheutwinkel, M., 1987. Screening of the food additive propionic acid for genotoxic properties, Fd. Chem. Toxic. 25:287-290).

6.2 EXEMPTION FROM TOLERANCE:

Supporting Decision by the Environmental Protection Agency, Office of Pesticide Programs to grant an Exemption from Tolerence:
In the Federal Register , August 4, 2004 [(Volume 69, Number 149), Rules and Regulations, pages 47022-47025] a Final Rule was announced. This regulation establishes an exemption from the requirement for tolerance for residues of propanoic (propionic) acid and its calcium and sodium salts on alll raw agricultural commodities, ...and reorganizes current tolerance exemptions. The action was initiated by a company interested in only three crops sugar beets, potatoes and sweet potatoes under the Food , Drug, and Cosmetic Act (FFDCA), as ammended by the Food Quality Protection Act of 1996. The EPA reviewed the existing data relative to human health and published a proposed rule persuant to section 408 of FFDCA. The expanded rule presented in this Federal Register notice establishes a broad exemption for tolerance for any residues of propanoic (or propionic) acid and the respective calcium and sodium salts on all crops when the chemicl is used as a fungicide or as an inert inredient in pesticides.

I U C L I D

D a t a s e t

Existing Chemical	Substance ID: 4075–81–4
CAS No.	4075–81–4
EINECS Name	calcium dipropionate
EINECS No.	223–795–8
Molecular Formula	C3H6O2.1/2Ca

Dataset created by: EUROPEAN COMMISSION – European Chemicals Bureau

This dossier is a compilation based on data reported by the European Chemicals Industry following 'Council Regulation (EEC) No. 793/93 on the Evaluation and Control of the Risks of Existing Substances'. All (non–confidential) information from the single datasets, submitted in the IUCLID/HEDSET format by individual companies, was integrated to create this document.

The data have not undergone any evaluation by the European Commission.

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1.0.1 OECD and Company Information

-

1.0.2 Location of Production Site

-

1.0.3 Identity of Recipients

-

1.1 General Substance Information

Substance type: inorganic
Physical status: solid

Substance type: organic
Physical status: solid

1.1.1 Spectra

-

1.2 Synonyms

Bioban-C
Source: BASF AG Ludwigshafen

Calcium dipropionate
Source: BASF AG Ludwigshafen

Calcium propanoate
Source: BASF AG Ludwigshafen

Calcium propionate
Source: BASF AG Ludwigshafen

Luprosil Spezial
Source: BASF AG Ludwigshafen

Propanoic acid, calcium salt (9CI)
Source: BASF AG Ludwigshafen

Propionic Acid, Calcium Salt
Source: Verdugt B.V. Tiel

Propionic acid, calcium salt (8CI)
Source: BASF AG Ludwigshafen

1.3 Impurities

-

1.4 Additives

-

1.5 Quantity

-

1.6.1 Labelling

-

1.6.2 Classification

-

1.7 Use Pattern

-

1.7.1 Technology Production/Use

-

1.8 Occupational Exposure Limit Values

Type of limit: MAK (DE)
Limit value:
Remark: Kein MAK-Wert festgelegt.
Source: BASF AG Ludwigshafen

(1)

1.9 Source of Exposure

-

1.10.1 Recommendations/Precautionary Measures

-

1.10.2 Emergency Measures

-

1.11 Packaging

-

1.12 Possib. of Rendering Subst. Harmless

-

1.13 Statements Concerning Waste

-

1.14.1 Water Pollution

Classified by: other: BASF
Labelled by: other: BASF
Class of danger: 1 (weakly water polluting)
Source: BASF AG Ludwigshafen

Classified by: other: BASF (calculated)
Labelled by:
Class of danger: 1 (weakly water polluting)
Source: BASF AG Ludwigshafen

1.14.2 Major Accident Hazards

Legislation: Stoerfallverordnung (DE)
Substance listed: no
Source: BASF AG Ludwigshafen

(2)

1.14.3 Air Pollution

-

1.15 Additional Remarks

-

1.16 Last Literature Search

-

1.17 Reviews

-

1.18 Listings e.g. Chemical Inventories

-

2.1 Melting Point

Value:
Remark: Thermische Zersetzung: ca. 245 Grad C
Source: BASF AG Ludwigshafen

(3)

2.2 Boiling Point

-

2.3 Density

Type: bulk density
Value: ca. 400 kg/m3
Source: BASF AG Ludwigshafen

(3)

2.3.1 Granulometry

-

2.4 Vapour Pressure

-

2.5 Partition Coefficient

-

2.6.1 Water Solubility

Value: = 260 g/l at 20 degree C
pH: 9.2 at 200 g/l and 20 degree C
Source: BASF AG Ludwigshafen

(3)

2.6.2 Surface Tension

-

2.7 Flash Point

-

2.8 Auto Flammability

Value: > 200 degree C
Remark: Pruefung auf Selbstentzuendung mit 400 cm3 im Drahtkorb:
- Induktionszeit / Lagerzeit: 1 h, 30 min.
- Exotherme Reaktion bei 200 Grad C.
- Temperaturerhoehung in Grad C: 2.

Source: BASF AG Ludwigshafen

(4)

Value:
Remark: Zuendtemperatur: 490 Grad C.
Source: BASF AG Ludwigshafen

(3)

2.9 Flammability

-

2.10 Explosive Properties

Result:
Remark: staubexplosionsfaehig
Source: BASF AG Ludwigshafen

(3)

2.11 Oxidizing Properties

-

2.12 Additional Remarks

-

3.1.1 Photodegradation

Type: other
Method:
Year: **GLP:**
Test substance:
Remark: K=1.60E-12 cm3/mol*s; gemessen mit AOP nach Meylan bei 298 K (Messwert fuer freie Saeure)
K=1.22E-12 cm3/mol*s; gemessen mit AOP nach Meylan bei 298 K (Messwert fuer freie Saeure)
Source: BASF AG Ludwigshafen
(5) (6)

3.1.2 Stability in Water

Type:
Method: other
Year: **GLP:**
Test substance:
Remark: no data are available
Source: BASF AG Ludwigshafen

3.1.3 Stability in Soil

Type: other **Radiolabel:**
Concentration:
Cation exch. capac.
Microbial biomass:
Method:
Year: **GLP:**
Test substance:
Remark: no data are available
Source: BASF AG Ludwigshafen

3.2 Monitoring Data (Environment)

Type of measurement:
Medium: food
Remark: The calcium salt of propionic acid is widely used as mold and rope inhibitors in bread and bakery products at levels of ca. 2000 ppm. The propionates have also found use in the prevention of mold in certain cheeses and on certain fruit and vegetable products.
Source: BASF AG Ludwigshafen
(7)

3.3.1 Transport between Environmental Compartments

Type: other
Media:
Method:
Year:
Remark: no data are available
Source: BASF AG Ludwigshafen

3.3.2 Distribution

Media: other
Method:
Year:
Remark: no data are available
Source: BASF AG Ludwigshafen

3.4 Mode of Degradation in Actual Use

Remark: no data are available
Source: BASF AG Ludwigshafen

3.5 Biodegradation

Type: aerobic
Inoculum: other: Belebtschlamm
Concentration: 300 mg/l related to DOC (Dissolved Organic Carbon)
Degradation: = 100 % after 7 day
Kinetic: 3 hour(s) = 18 %
Method: OECD Guide-line 302 B "Inherent biodegradability: Modified Zahn-Wellens Test"
Year: **GLP:**
Test substance:
Remark: Das Produkt ist biologisch abbaubar.
Source: BASF AG Ludwigshafen

(8)

Type: aerobic
Inoculum:
Degradation: < 1 % after 5 day
Method: other: BOD5-Test
Year: **GLP:**
Test substance:
Source: BASF AG Ludwigshafen

(8)

3.6 BOD5, COD or BOD5/COD Ratio

Method: other

C O D

Method: other
COD: = 1110 mg/g substance

R A T I O B O D 5 / C O D

BOD5/COD: < .008

Remark: BSB5 <2 mg/g
Source: BASF AG Ludwigshafen

(8)

3.7 Bioaccumulation

Species: other
Exposure period:
Concentration:
BCF:
Elimination:
Method:
Year: **GLP:**
Test substance:
Remark: no data are available
Source: BASF AG Ludwigshafen

3.8 Additional Remarks

-

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type: static
Species: Leuciscus idus (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:** no
NOEC: = 5000
LC0: = 5000
LC50: > 10000
LC100: > 10000
Method: other: Bestimmung der Wirkung von Wasserinhaltsstoffen auf Fische, DIN38412 Teil 15
Year: 1982 **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Remark: 10000mg/l: lethality 2/10 after 96H
5000mg/l: no lethality
No toxic symptoms detectable.
Source: BASF AG Ludwigshafen

(9)

Type: static
Species: Leuciscus idus (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:** no
NOEC: = 5000
LC0: = 5000
LC50: > 10000
LC100: > 10000
Method: other: Bestimmung der Wirkung von Wasserinhaltsstoffen auf Fische,DIN38412 Teil 15
Year: 1982 **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Remark: 10000mg/l: lethality 2/10 after 96H
5000mg/l: no lethality
No toxic symptoms detectable.
Source: BASF AG Ludwigshafen

(9)

Type:
Species: Cyprinus carpio (Fish, fresh water)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:**
LC50: = 72
Method:
Year: **GLP:**
Test substance:
Remark: LC50 24h: 95mg/l.
Japanese article with abstract and figures in english.
Source: BASF AG Ludwigshafen

(10) (11)

Type:
Species: Lepomis macrochirus (Fish, fresh water)
Exposure period: 24 hour(s)
Unit: mg/l **Analytical monitoring:**
LC50: = 188
Method:
Year: **GLP:**
Test substance:
Source: BASF AG Ludwigshafen
(12) (13) (14)

Type:
Species: Lepomis macrochirus (Fish, fresh water)
Exposure period: 24 hour(s)
Unit: mg/l **Analytical monitoring:**
LC50: = 5000
Method:
Year: **GLP:**
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate
(14)

4.2 Acute Toxicity to Aquatic Invertebrates

Species: Daphnia magna (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l **Analytical monitoring:** no
EC0: = 250
EC50: > 500
EC100: > 500
Method: Directive 84/449/EEC, C.2 "Acute toxicity for Daphnia"
Year: 1989 **GLP:** no
Test substance:
Source: BASF AG Ludwigshafen
(15)

Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** no
EC0: = 250
EC50: > 500
EC100: > 500
Method: Directive 84/449/EEC, C.2 "Acute toxicity for Daphnia"
Year: 1989 **GLP:** no
Test substance:
Source: BASF AG Ludwigshafen
(15)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: Scenedesmus subspicatus (Algae)
Endpoint:
Exposure period: 72 hour(s)
Unit: mg/l **Analytical monitoring:** no
EC50: > 500
EC20 : > 500
Method: OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year: 1988 **GLP:** no
Test substance:
Source: BASF AG Ludwigshafen

(15)

4.4 Toxicity to Microorganisms e.g. Bacteria

Type: aquatic
Species: Pseudomonas putida (Bacteria)
Exposure period: 17 hour(s)
Unit: mg/l **Analytical monitoring:** no
EC0: = 350
EC10: = 350
EC50: = 510
EC90 : = 1600
Method: other: DIN 38 412/8, Zellvermehrungshemmtest
Year: 1989 **GLP:** no
Test substance:
Source: BASF AG Ludwigshafen

(15)

Type:
Species: other bacteria: Belebtschlamm
Exposure period: 30 minute(s)
Unit: mg/l **Analytical monitoring:**
EC0: = 1000
Method: ISO 8192 "Test for inhibition of oxygen consumption by activated sludge"
Year: **GLP:**
Test substance:
Remark: Bei sachgemaesser Einleitung in adaptierte biologische Klaeranlagen sind keine Stoerungen der Abbauaktivitaet des Belebtschlamms zu erwarten.
Source: BASF AG Ludwigshafen

(8)

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

Species: Salmo gairdneri (Fish, estuary, fresh water)
Endpoint:
Exposure period:
Unit: **Analytical monitoring:**
Method: other: BASF Test
Year: **GLP:** no
Test substance: as prescribed by 1.1 – 1.4
Remark: The treatment of about 9 month old rainbow trouts (60 animals per group, both sexes) with 0,5%; 1% and 1,5% propionic acid in pellet–feed for 7 weeks caused a dose–dependent loss of body– weight up to 23,1% in the high dose group in comparison to untreated control.
The histopathology of 5 animals out of each group revealed a more pronounced expression of viscerale granulomas with increasing concentration, but large interindividuel variations. The viscerale granuloma syndrom in combination with nephrocalcinoses is reported to be of polyfactorial etiology.
Source: BASF AG Ludwigshafen

(16)

4.5.2 Chronic Toxicity to Aquatic Invertebrates

Species: other
Endpoint:
Exposure period:
Unit: **Analytical monitoring:**
Method:
Year: **GLP:**
Test substance:
Remark: no data are available
Source: BASF AG Ludwigshafen

TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Soil Dwelling Organisms

Type: other
Species:
Endpoint:
Exposure period:
Unit:
Method:
Year: **GLP:**
Test substance:
Remark: no data are available
Source: BASF AG Ludwigshafen

4.6.2 Toxicity to Terrestrial Plants

Species:
Endpoint:
Expos. period:
Unit:
Method: other
Year: **GLP:**
Test substance:
Remark: no data are available
Source: BASF AG Ludwigshafen

4.6.3 Toxicity to other Non–Mamm. Terrestrial Species

Species: other
Endpoint:
Expos. period:
Unit:
Method:
Year: **GLP:**
Test substance:
Remark: no data are available
Source: BASF AG Ludwigshafen

4.7 Biological Effects Monitoring

Remark: no data are available
Source: BASF AG Ludwigshafen

4.8 Biotransformation and Kinetics

Type: other
Remark: no data are available
Source: BASF AG Ludwigshafen

4.9 Additional Remarks

Source: BASF AG Ludwigshafen

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: = 3470 mg/kg bw
Method: other: BASF-Test
Year: **GLP:** no
Test substance: other TS
Remark: apathy or restlessness, dyspnoea, partly cyanosis and accumulation of liquid in abdomen
Source: BASF AG Ludwigshafen
Test substance: Propionic acid

(17)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: = 4290 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Remark: no further information
Source: BASF AG Ludwigshafen

(18) (19) (20) (21)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: > 400 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Remark: 1%aqueous solution.
Source: BASF AG Ludwigshafen

(18) (22)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: = 5160 mg/kg bw
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 – 1.4
Source: BASF AG Ludwigshafen
(18) (23) (19)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: = 2600 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Source: BASF AG Ludwigshafen
(24)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: 3920 – 4380 mg/kg bw
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 – 1.4
Remark: LD50 male rats: 4280 or 4380 mg/kg
LD50 female rats: 3920 or 4040 mg/kg
Source: BASF AG Ludwigshafen
(25)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: ca. 6400 mg/kg bw
Method: other: BASF–Test
Year: **GLP:** no
Test substance: as prescribed by 1.1 – 1.4
Remark: Symptoms: dyspnoea, apathy, abdominal position, piloerection Pathology: adhesion of stomach wall and liver
Source: BASF AG Ludwigshafen
(26)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: ca. 6500 mg/kg bw
Method: other: BASF–Test
Year: **GLP:** no
Test substance: as prescribed by 1.1 – 1.4
Remark: Symptoms: dyspnoes, apathy; pathology without findings.
Source: BASF AG Ludwigshafen
(27)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: 3920 – 4380 mg/kg bw
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 – 1.4
Remark: LD50 male rats: 4280 or 4380 mg/kg
LD50 female rats: 3920 or 4040 mg/kg
Source: BASF AG Ludwigshafen
(25) (28)

Type: LD50
Species: mouse
Sex:
Number of Animals:
Vehicle:
Value: = 5100 mg/kg bw
Method:
Year: **GLP:**
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate
(18) (23) (19)

Type: LD50
Species: mouse
Sex:
Number of Animals:
Vehicle:
Value: 2350 – 2900 mg/kg bw
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 – 1.4
Remark: LD50 male mice: 2350 or 2600 mg/kg
LD50 female mice: 2400 or 2900 mg/kg
Another value of 3340 mg/kg is cited from unidentifiable literature.

Source: BASF AG Ludwigshafen
(25)

Type: LD50
Species: mouse
Sex:
Number of Animals:
Vehicle:
Value: 2350 – 2900 mg/kg bw
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 – 1.4
Remark: LD50 male mice: 2350 or 2600 mg/kg
LD50 female mice: 2400 or 2900 mg/kg
Another value of 3340 mg/kg is cited from unidentifiable literature.
Source: BASF AG Ludwigshafen
(25) (28)

Type: LD50
Species: rabbit
Sex:
Number of Animals:
Vehicle:
Value: ca. 695 mg/kg bw
Method: other: BASF–Test
Year: **GLP:** no
Test substance: other TS
Remark: symptoms: lack of appetite, at doses above LD50 dyspnoea, atonia and staggering.
Source: BASF AG Ludwigshafen
Test substance: Propionic acid
(29)

5.1.2 Acute Inhalation Toxicity

Type: LC50
Species: rat
Sex:
Number of Animals:
Vehicle:
Exposure time: 1 hour(s)
Value: > 19.7 mg/l
Method: other: BASF–Test
Year: **GLP:** no
Test substance: other TS
Remark: vapor–exposure, LC50 > 4,9 mg/l/4h (converted with Habers–rule) irritation of respiratory system, corneal opacities
Source: BASF AG Ludwigshafen
Test substance: Propionic acid
(30)

Type: LC50
Species: rat
Sex:
Number of Animals:
Vehicle:
Exposure time: 4 hour(s)
Value: > 5.4 mg/l
Method: other: BASF-Test
Year: **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Source: BASF AG Ludwigshafen

(31)

Type: LC50
Species: rat
Sex:
Number of Animals:
Vehicle:
Exposure time: 4 hour(s)
Value: > 5.4 mg/l
Method: other: BASF-Test
Year: **GLP:** no
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Sodiumpropionate, dust aerosol;

(32)

Type: LC50
Species: rat
Sex:
Number of Animals:
Vehicle:
Exposure time: 4 hour(s)
Value: > 4.9 mg/l
Method: other: BASF Test
Year: **GLP:** no
Test substance: other TS
Remark: vapor-exposure, (converted with Habers-rule) irritation of respiratory system, corneal opacities
Source: BASF AG Ludwigshafen
Test substance: Propionic acid

(30)

Type: LC50
Species: rat
Sex:
Number of Animals:
Vehicle:
Exposure time: 1 hour(s)
Value: > 19.7 mg/l
Method: other: BASF-Test
Year: **GLP:** no
Test substance: other TS
Remark: vapor-exposure, LC50 > 4,9 mg/l/4h (converted with Habers-rule) irritation of respiratory system, corneal opacities
Source: BASF AG Ludwigshafen
Test substance: Propionic acid

(33)

Type: LC50
Species: rat
Sex:
Number of Animals:
Vehicle:
Exposure time: 4 hour(s)
Value: > 4.9 mg/l
Method: other: BASF Test
Year: **GLP:** no
Test substance: other TS
Remark: vapor-exposure, (converted with Habers-rule) irritation of respiratory system, corneal opacities
Source: BASF AG Ludwigshafen
Test substance: Propionic acid

(33)

Type: other: IRT
Species: rat
Sex:
Number of Animals:
Vehicle:
Exposure time: 8 hour(s)
Value:
Method:
Year: **GLP:**
Test substance:
Remark: No mortality after 8 h exposure to an atmosphere enriched or saturated at 20 degree C. (0/6 rats)
Source: BASF AG Ludwigshafen

(20) (21)

Type: other: IRT
Species: rat
Sex:
Number of Animals:
Vehicle:
Exposure time: 7 hour(s)
Value:
Method: other: in Anlehnung an die von H.F. Smith et al: Am.Ind.Hyg.Ass.J. 23,95-107 (1962) beschriebene Methode durchgefuehrt
Year: 1962 **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Remark: mortality 0/12 rats after 7 hours
Source: BASF AG Ludwigshafen

(34)

Type: other: IRT
Species: rat
Sex:
Number of Animals:
Vehicle:
Exposure time: 7 hour(s)
Value:
Method: other: in Anlehnung an die von H.F. Smith et al: Am.Ind.Hyg.Ass.J.23,95-107 (1962) beschriebene Methode durchgefuehrt
Year: 1962 **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Remark: mortality 0/12 rats after 7 hours
Source: BASF AG Ludwigshafen

(34)

Type:
Species: rat
Sex:
Number of Animals:
Vehicle:
Exposure time:
Value:
Method:
Year: **GLP:**
Test substance:
Remark: Acute inhalation studies with 5000, 2000, 800, 100 and 23mg/m3 propionic acid yielded irritant effects in the upper 3 concentrations and no effects at 100 and 23 mg/m3. Obviously no mortality occured. The somewhat confuse description of systemic effects is not useable.
Source: BASF AG Ludwigshafen

(35)

5.1.3 Acute Dermal Toxicity

Type: LD50
Species: rabbit
Sex:
Number of Animals:
Vehicle:
Value: = 500 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Remark: no further information
Source: BASF AG Ludwigshafen

(19) (20) (21)

Type: LD50
Species: rabbit
Sex:
Number of Animals:
Vehicle:
Value: = 500 mg/kg bw
Method:
Year: **GLP:**
Test substance: other TS
Remark: no further information
Source: BASF AG Ludwigshafen
Test substance: Propionic acid

(19) (20) (21)

5.1.4 Acute Toxicity, other Routes

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.p.
Value: 200 – 400 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Remark: 1% aqueous solution.
Source: BASF AG Ludwigshafen

(22)

Type:
Species: cat
Sex:
Number of Animals:
Vehicle:
Route of admin.: s.c.
Value: 1000 mg/kg bw
Method:
Year: **GLP:**
Test substance: other TS
Remark: Sleep
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate

(36)

Type:
Species: dog
Sex:
Number of Animals:
Vehicle:
Route of admin.: s.c.
Value: 925 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Remark: Total dose 14,8 g. 1,05 g propionic acid excreted in urine. No abnormalities detected.
Source: BASF AG Ludwigshafen

(36)

Type: LD50
Species: mouse
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.v.
Value: = 625 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Remark: 10 % aqueous solution
Source: BASF AG Ludwigshafen

(37)

Type:
Species: rabbit
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.v.
Value: 1320 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Remark: Lethal dose.
Source: BASF AG Ludwigshafen

(36)

Type:
Species: rabbit
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.v.
Value: 2200 mg/kg bw
Method:
Year: **GLP:**
Test substance: other TS
Remark: Sedation or narcosis for about 1h, afterwards no abnormalities
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate

(36)

Type:
Species: dog
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.v.
Value: 570 mg/kg bw
Method:
Year: **GLP:**
Test substance: other TS
Remark: dullness, narcosis, vomiting
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate

(36)

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result: corrosive
EC classificat.:
Method: other: BASF-Test
Year: **GLP:** no
Test substance: other TS
Remark: Necrosis after exposure periods of 5 and 15 minutes but not after 1 minute.
Source: BASF AG Ludwigshafen
Test substance: Propionic acid

(38)

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result: corrosive
EC classificat.:
Method: other: DOT Methode were conducted in accordance with 19 CFR, Chapter I,Sec, 173.40 as amendment in Federal Register, Vol. 37, No. 57, March 23,1972.
Year: 1972 **GLP:**
Test substance:
Remark: DOT-Method, 4h occlusive application to intact and abraded skin
Source: BASF AG Ludwigshafen

(39)

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result:
EC classificat.:
Method:
Year: **GLP:**
Test substance:
Remark: 15% solution of propionic acid in water, not corrosive

Source: BASF AG Ludwigshafen (40)

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result:
EC classificat.:
Method:
Year: **GLP:**
Test substance:
Remark: Irritant, grade 6 of 10
Source: BASF AG Ludwigshafen (19) (41) (42)

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result:
EC classificat.:
Method:
Year: **GLP:**
Test substance:
Remark: Local damage may occur to skin on contact with concentrated solutions of propionic acid.
Source: BASF AG Ludwigshafen (22)

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result: not irritating
EC classificat.:
Method: Draize Test
Year: 1973 **GLP:** no
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Calciumpropionate feed grade, sodiumpropionate (43)

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result: irritating
EC classificat.:
Method:
Year: **GLP:**
Test substance:
Remark: Mild skin irritation was seen following 4 h closed contact of the skin with a 2.5 % aqueous solution, mild to moderate irritation occured with 25 % solutions, while moderate to severe irritation and corrosion were seen at concentrations of 40 % and above.
Source: BASF AG Ludwigshafen

(44)

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result: corrosive
EC classificat.:
Method: other: DOT Methode were conducted in accordance with 19 CFR, ChapterI,Sec, 173.40 as amendment in Federal Register, Vol. 37, No. 57, March23,1972.
Year: 1972 **GLP:**
Test substance:
Remark: DOT–Method, 4h occlusive application to intact and abraded skin
test substance probably propionic acid
Source: BASF AG Ludwigshafen

(39)

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result:
EC classificat.:
Method:
Year: **GLP:**
Test substance:
Remark: Irritant, grade 6 of 10
Source: BASF AG Ludwigshafen

(19) (41) (42)

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result:
EC classificat.:
Method:
Year: **GLP:**
Test substance: other TS
Remark: Local damage may occur to skin on contact with concentrated solutions of propionic acid.
Source: BASF AG Ludwigshafen
Test substance: propionic acid

(22)

Species: mammal
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result:
EC classificat.:
Method:
Year: **GLP:**
Test substance: other TS
Remark: species: dog and cat, irritation
depending on pH of solution: alkaline pH (8,4) irritant (like bicarbonate), neutral pH not irritant.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate

(45)

5.2.2 Eye Irritation

Species: rabbit
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result: not irritating
EC classificat.:
Method:
Year: **GLP:**
Test substance: other TS
Remark: Sodium propionate, 20% solution, no description of method.

Source: BASF AG Ludwigshafen
Test substance: Sodium propionate
(45)

Species: rabbit
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result:
EC classificat.:
Method:
Year: **GLP:**
Test substance:
Remark: Irritant, grade 9 of 10
Source: BASF AG Ludwigshafen
(19) (41) (21)

Species: rabbit
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result: not irritating
EC classificat.:
Method: Draize Test
Year: 1973 **GLP:** no
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Calciumpropionate feed grade, sodiumpropionate
(43)

Species: rat
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result:
EC classificat.:
Method:
Year: **GLP:**
Test substance:
Remark: In a 4 h inhalation study atmospheric concentrations of around 5 mg/l propionic acid produced slight eye irritation during, and several hours after exposure.
Source: BASF AG Ludwigshafen
(46)

5.3 Sensitization

Type: Guinea pig maximization test
Species: guinea pig
Number of Animals:
Vehicle:
Result: not sensitizing
Classification:
Method: other: according to the method described by Magnusson and Kligmann"Allergie contact dermatitis in the guinea pig" Ed. Ch.C. Thomas,Springfield, Illinois, USA (1970)
Year: 1970 **GLP:** no
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Calcium- and sodiumpropionate

(47)

Type: Guinea pig maximization test
Species: guinea pig
Number of Animals:
Vehicle:
Result: not sensitizing
Classification:
Method: other: according to the method described by Magnusson and Kligmann: "Allergic contact dermatitis in the guinea pig"; Ed.: Ch.C.Thomas, Springfield, Illinois, USA
Year: 1970 **GLP:** no
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Calcium- and sodiumpropionate

(47)

5.4 Repeated Dose Toxicity

Species: rat **Sex:** male
Strain: Wistar
Route of admin.: inhalation
Exposure period: 3-4 weeks
Frequency of treatment: "continuous exposure"
Post. obs. period:
Doses: 23 and 100 mg/m3
Control Group:
Method:
Year: **GLP:**
Test substance:
Remark: Due to major deficiencies in presentation of the data the study is considered to be not valid.
Result: Changes in lung tissue, bronchitis, peribronchitis, desquamation. The confuse presentation of further systemic effects is not usable.
Source: BASF AG Ludwigshafen

(35)

Species: rat **Sex:**
Strain: Wistar
Route of admin.: inhalation
Exposure period: 3-month
Frequency of treatment:
Post. obs. period:
Doses: 0,017; 0,17; 1,7 mg/m3
Control Group: yes
NOAEL: 1700 mg/l
Method:
Year: **GLP:**
Test substance:
Remark: Due to major deficiencies in presentation of the data the study is considered to be not valid.
Result: No morphological changes.
The clinical findings are undistinguishable confused with acute and subacute (?) studies.
Source: BASF AG Ludwigshafen

(35)

Species: rat **Sex:** male
Strain: Wistar
Route of admin.: inhalation
Exposure period: 3-4 weeks
Frequency of treatment: "continuous exposure"
Post. obs. period:
Doses: 0.023 and 0.100 mg/l
Control Group:
Method:
Year: **GLP:**
Test substance:
Remark: Due to major deficiencies in presentation of the data the study is considered to be not valid.
Result: Changes in lung tissue, bronchitis, peribronchitis, desquamation. The confuse presentation of further systemic effects is not usable.
Source: BASF AG Ludwigshafen

(35)

Species: rat **Sex:**
Strain: Wistar
Route of admin.: inhalation
Exposure period: 3-month
Frequency of treatment:
Post. obs. period:
Doses: 1.7x10E-5, 1.7x10E-4, 1.7x10E-3 mg/l
Control Group: yes
NOAEL: 1700 mg/l
Method:
Year: **GLP:**
Test substance:
Remark: Due to major deficiencies in presentation of the data the study is considered to be not valid.
Result: No morphological changes.
The clinical findings are undistinguishable confused with acute and subacute (?) studies.
Source: BASF AG Ludwigshafen

(35)

Species: rat **Sex:** male/female
Strain: Sprague-Dawley
Route of admin.: oral feed
Exposure period: 90 days
Frequency of treatment: daily
Post. obs. period: 42 days, 10 rats per sex of control, 6200 and 50000ppm groups
Doses: 6200, 12500, 25000, 50000ppm (=517;1042;2083;4167mg/kg b.w.)
Control Group: yes, concurrent no treatment
NOAEL: 6200 ppm
Method: other: BASF-Test
Year: **GLP:** no
Test substance: other TS
Result: 20 rats per sex and dosage, 10 rats per sex and dosage for post- exposure-observation-period
50000ppm: feed intake and body weight gain of male animals reduced, no other clinical, hematological or clinicochemical effects, single slight deviations of absolute and relative organ weights without pathological significance, no macroscopic findings, proliferation-acanthosis and retention-hyperceratosis of forestomach mucosa. Reversibility in post-exposure-observation-period. 25000 and 12500ppm: dose-dependent occurance of forestomach- lesions as in the high dosage group, no significant other effects.
Source: BASF AG Ludwigshafen
Test substance: Propionsaeure technisch

(18) (48)

Species: rat **Sex:** male/female
Strain: Sprague-Dawley
Route of admin.: oral feed
Exposure period: 28 days
Frequency of treatment: daily
Post. obs. period:
Doses: 10000, 20000, 50000ppm
Control Group: yes, concurrent no treatment
Method: other: BASF-Test
Year: **GLP:** no
Test substance: other TS
Result: 10 rats per sex and dosage group. Substance intake approx. 800, 1500 and 3900 mg/kg b.w. (Calc. from feed consumption). 50000 ppm: decrease in weight gain of the male animals, no other clinical, hematological or clinicochemical effects, decrease in absolute liverweight of male animals, no change in relative organweights, histologically detected proliferation-acanthosis and retention-hyperceratosis of the forestomach mucosa. 20000 and 10000 ppm: dose-dependent occurence of mucosal lesions of forestomach, no other symptoms.
Source: BASF AG Ludwigshafen
Test substance: Propionsaeure technisch

(18) (49)

Species: rat **Sex:** male
Strain: Sprague-Dawley
Route of admin.: oral feed
Exposure period: 30 days
Frequency of treatment: daily
Post. obs. period:
Doses: 4% (=40000ppm)
Control Group: yes, concurrent no treatment
Method:
Year: **GLP:**
Test substance: other TS
Remark: Study was performed in order to assess the onset of lesions in the forestomach.
Result: 5 rats per sacrifice, sacrifices on days 2,4,7,10,14,22 and 30. Mean substance intake 3370mg/kg b.w. (calculated from feed intake).
No treatment related clinical findings. Pathology restricted to the forestomach. Macroscopic lesions from day ten onward, prominent limiting ridge and visible mucosal alterations. Histopathology: From day 2 onward acanthosis and hyperkeratosis, from day 14 basal cell hyperplasia. Ulcer in 1 rat and polyplike lesions in 3 animals after 22 and 30 days.
Source: BASF AG Ludwigshafen
Test substance: Propionic acid

(50)

Species: rat **Sex:**
Strain:
Route of admin.: oral feed
Exposure period: 3-4 weeks
Frequency of treatment:
Post. obs. period:
Doses: 1 and 3% (10000 and 30000ppm = 830 and 2490mg/kg)
Control Group: yes, concurrent no treatment
Method:
Year: **GLP:**
Test substance: other TS
Result: The application of 1% sodium or calcium propionate in feed for 4 weeks or of 3% of the substances for 3 weeks did not reduce weight gain in comparison to the control animals. No other parameters determined.
Source: BASF AG Ludwigshafen
Test substance: Sodium and Calcium propionate

(51)

Species: rat **Sex:** male
Strain: Fischer 344
Route of admin.: oral feed
Exposure period: 9, 15, 21, 27 days
Frequency of treatment: daily
Post. obs. period:
Doses: 4% (40000ppm = 3320mg/kg)
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Result: The incorporation of Methyl-H3-Thymidine into the mucosa of the forestomach was not influenced after 9 and 15 days but was enhanced after 21 and 28 days of treatment. Macroscopic and histologic lesions (general and nodular mucosal thickening) were observed in the forestomach after 27 days.
Source: BASF AG Ludwigshafen

(52)

Species: rat **Sex:** male/female
Strain: other: albino, mongrels
Route of admin.: oral feed
Exposure period: 110 days
Frequency of treatment: daily
Post. obs. period:
Doses: about 5% (50000ppm = 3300mg/kg)
Control Group:
Method:
Year: **GLP:**
Test substance:
Result: 5 rats.
No systemic toxicity.
1/5 early death. 3/4 umbilicate or warty lesions of forestomach mucosa, 1/4 no abnormalities. Hyperkeratosis and hyperplasia of forestomach mucosa. No lesions in the glandular stomach. Similar effects after treatment with butyric acid (even more effective) and valeric acid.
Source: BASF AG Ludwigshafen

(18) (53)

Species: rat **Sex:** female
Strain: other: Wistar (SLC)
Route of admin.: oral feed
Exposure period: 1 year
Frequency of treatment: daily
Post. obs. period:
Doses: 2% (20000ppm = 1320mg/kg), calculated total intake 185g/animal
Control Group: yes, concurrent no treatment
NOAEL: 2 %
Method:
Year: **GLP:**
Test substance: other TS
Result: Very slight retardation of growth rate (b.w. at the end of the study 290g versa 291g in control). No hematological, clinicochemical or urinalytic changes. No changes in organ weights. Histopathology: different spontaneous findings without substance relation, thereof 2 mammary tumours and 1 myxoma of the uterus. These findings are considered to be not substance related because in a test group fed simultaniously with 2% sodium propionate and 5% sorbic acid no such changes occured.
Source: BASF AG Ludwigshafen
Test substance: sodium propionate, 40 animals

(18) (54) (55)

Species: rat **Sex:** male/female
Strain: Wistar
Route of admin.: oral feed
Exposure period: 1 year
Frequency of treatment: daily
Post. obs. period:
Doses: The animals were maintained on a feed consisting in 75% bread which wasbaked under addition of the 50 fold amount of 4 bread additives andbleached flour. One of the additives was 5% sodium propionate.
Control Group: yes
Method:
Year: **GLP:**
Test substance: other TS
Result: The animals were maintained on a feed consisting in 75% bread which was baked under addition of the 50 fold amount of 4 bread additives and bleached flour. One of the additives was 5% sodium propionate.
Interim sacrifices were performed and a number of organs were examined histologically. No clinical nor pathological effects were observed. Therefore the authors conclude that neither the single substances nor their mixture cause toxic effects. The complex mixture of substances and conduct of the study make it difficult to judge on the real effect, if at all for single substances.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate, 27 animals per sex

(18) (22) (56) (19)

Species: rat **Sex:** male
Strain: Wistar
Route of admin.: oral feed
Exposure period: 32 weeks
Frequency of treatment: daily
Post. obs. period:
Doses: The animals were maintained on a feed consisting in 75% of a bakiingmixture for bread which contained the 50 fold amount of 4 bread additivesand bleached flour. One of the additives was 5% sodium propionate.
Control Group: yes
Method:
Year: **GLP:**
Test substance: other TS
Result: The animals were maintained on a feed consisting in 75% of a baking mixture for bread which contained the 50 fold amount of 4 bread additives and bleached flour. One of the additives was 5% sodium propionate.
Groups fed with diets containing 5% propionate show a reduction in body weight gain but no substance related histopathological effects were observed. The study was furthermore complicated by infections in different testgroups. The complex mixture of substances and conduct of the study make it difficult to judge on the real effect, if

at all for single substances.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate, 30 animals

(18) (57)

Species: rat **Sex:** male/female
Strain: Wistar
Route of admin.: oral feed
Exposure period: f 4 weeks, m 8 weeks
Frequency of treatment: daily
Post. obs. period: 1 group m 8 weeks
Doses: 4% (40000ppm = 3320mg/kg KGW)
Control Group: yes
Method:
Year: **GLP:**
Test substance: other TS
Result: Wistar Han/BGA, 5 animals/sex
Clinical examination and organ weights without abnormalities. Forestomach 4 week exposure: hyperkeratosis and hyperplasie of l limiting ridge, isolated ulcerations in 4/5 animals. Forestomach 8 week exposure: more pronounced lesions in number and expression.
Reversibility of changes in 8 week post exposure observation period.
Similar effects produced by 4 and 6% acetic acid or 4% capronic acid.
Source: BASF AG Ludwigshafen

(58) (59)

Species: rat **Sex:** male
Strain: Wistar
Route of admin.: oral feed
Exposure period: 4 weeks
Frequency of treatment: daily
Post. obs. period:
Doses: 4% (40000ppm = 3320mg/kg KGW)
Control Group: yes
Method:
Year: **GLP:**
Test substance: other TS
Result: Clinical examination and organ weights without abnormalities. Forestomach : limiting ridge slightly thickend in 3/5, mucosa macroscopically unchanged.
Histology: hyperkeratosis of mucosa, hyperplasia of basal cells at the limiting ridge in 1/5. In general obviously slighter forestomach-changes as compared to the acid.
Similar effects produced by 4% Sodium acetate.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate, Wistar Han/BGA, 5 animals

(58) (60)

Species: rat **Sex:** male/female
Strain: Wistar
Route of admin.: oral feed
Exposure period: f 4 weeks, m 8 weeks
Frequency of treatment: daily
Post. obs. period:
Doses: 4% (40000ppm = 3320mg/kg KGW)
Control Group: yes
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 – 1.4
Result: Reduction of feed consumption, body weight gain and abs. organ weights.
Forestomach: 4 week exposure: Slight thickening of limiting ridge. Hyperkeratosis and hyperplasie of mucosa clearly far less pronounced compared to the acid.
Wistar Han/BGA, 5 animals/sex.
Source: BASF AG Ludwigshafen

(58) (60)

Species: rat **Sex:** male/female
Strain: other: Wistar Han/BGA
Route of admin.: oral feed
Exposure period: 90 days
Frequency of treatment: daily
Post. obs. period: 1 group for 0,1 or 4% respectively over 90 and 180 days
Doses: 0,2; 0,5; 1 and 4% (= 166, 415, 830, 3320mg/kg B.W.)
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Result: Wistar Han/BGA, 10 animals/sex.
Clinical and hematological examination and organ weights without abnormalities.
Forestomach males: hyperkeratosis and hyperplasia of mucosa, at 4% 1/10 atypical basal cell proliferation and 5/10 dysplasia. Forestomach females: hyperkeratosis and hyperplasia at 4% (hyperkeratosis also in controls) in differnt regions of forestomach. Effects largely reversible during 90–day post exposure observation period. After 180 days appearance of first agerelated changes in the forestomach.
NOEL: male: 0.2 %, female 1%
Source: BASF AG Ludwigshafen

(61)

Species: rat **Sex:** male
Strain:
Route of admin.: oral feed
Exposure period: 56 days
Frequency of treatment: daily
Post. obs. period:
Doses: 20000 and 40000ppm
Control Group: yes
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 – 1.4
Result: 30% and 70% soy protein diets were used which were partly supplemented with vitamin B12. Reduction in body weight occurred in comparison to the soy protein diets without propionate addition. This was more pronounced in the 30% diet and independent of vit. B12 supplementation.
No other toxicological parameters were investigated.
Source: BASF AG Ludwigshafen

(62)

Species: rat **Sex:** male/female
Strain: Wistar
Route of admin.: oral feed
Exposure period: 7 days
Frequency of treatment: continued
Post. obs. period: no
Doses: 4 % in diet
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Result: The test– and control groups consisted of 5 male and 5 female rats. No significant clinical signs were recorded during the treatment.
The stomach walls of the treated rats were occasionally thickened and the mucosal surface was discoloured in several animals. In the forestomach of treated rats acanthosis, epithelial vacuolation and oedema of the lamina propria were reported. In the limiting ridge an increased number of mitotic figures were seen.
Source: BASF AG Ludwigshafen

(63) (64)

Species: rat **Sex:** male/female
Strain: Wistar
Route of admin.: oral feed
Exposure period: 1 year
Frequency of treatment: daily
Post. obs. period:
Doses: The animals were maintained on a feed consisting in 75% bread whichwasbaked under addition of the 50 fold amount of 4 bread additivesandbleached flour. One of the additives was 5% sodium propionate.
Control Group: yes
Method:
Year: **GLP:**
Test substance: other TS
Result: The animals were maintained on a feed consisting in 75% bread which was baked under addition of the 50 fold amount of 4 bread additives and bleached flour. One of the additives was 5% sodium propionate.
Interim sacrifices were performed and a number of organs were examined histologically. No clinical nor pathological effects were observed. Therefore the authors conclude that neither the single substances nor their mixture cause toxic effects. The complex mixture of substances and conduct of the study make it difficult to judge on the real effect, if at all for single substances.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate, 27 animals per sex
(18) (22) (56) (19)

Species: rat **Sex:** male
Strain: Wistar
Route of admin.: oral feed
Exposure period: 32 weeks
Frequency of treatment: daily
Post. obs. period:
Doses: The animals were maintained on a feed consisting in 75% of abakiingmixture for bread which contained the 50 fold amount of 4 breadadditivesand bleached flour. One of the additives was 5% sodiumpropionate.
Control Group: yes
Method:
Year: **GLP:**
Test substance: other TS
Result: The animals were maintained on a feed consisting in 75% of a baking mixture for bread which contained the 50 fold amount of 4 bread additives and bleached flour. One of the additives was 5% sodium propionate.
Groups fed with diets containing 5% propionate show a reduction in body weight gain but no substance related histopathological effects were observed. The study was furthermore complicated by infections in different testgroups. The complex mixture of substances and conduct of the study make it difficult to judge on the real effect, if

at all for single substances.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate, 30 animals

(18) (57)

Species: rat **Sex:** male
Strain: Wistar
Route of admin.: gavage
Exposure period: 1; 3; 7; 14 or 28 days
Frequency of treatment: daily
Post. obs. period: no
Doses: 300 mg/kg
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Result: No treatment related findings in the forestomach were found after 1 and 3 days of treatment.
After 7 and more days of treatment thickening of the forestomach mucosa respectively hyperplasia of the squamous epithelium with marked desquamation were found.
Source: BASF AG Ludwigshafen

(65)

Species: mouse **Sex:** male/female
Strain: B6C3F1
Route of admin.: oral feed
Exposure period: 7 days
Frequency of treatment: continued
Post. obs. period: no
Doses: 4 % in diet
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Result: Test and control groups consisted of 5 male and 5 female mice. No significant clinical signs were recorded during the treatment. One male and two female mice receiving propionic acid in diet had thick stomach walls. In forestomach basal cell hyperplasia and epithelial downgrowths were reported, no treatment-related findings were detected in the limiting ridge.
Source: BASF AG Ludwigshafen

(66) (64)

Species: mouse **Sex:** female
Strain: other: Crl:CD1(ICR)BR
Route of admin.: dermal
Exposure period: 90 days
Frequency of treatment: each working day
Post. obs. period: no
Doses: 50ul of 8%, 10% and 14% aqueous solution (133, 167, 233 mg/kg bw)
Control Group: yes
NOAEL: < 8 %
Method: OECD Guide-line 409 "Subchronic Oral Toxicity - Non-rodent: 90-day Study"
Year: 1981 **GLP:** yes
Test substance: other TS
Remark: At the beginning of the study the applied concentrations were 6%, 8% and 10%. When after 3 weeks of treatment no dermal effects occured the low concentration was increased to 14%.
Result: No influence of treatment on body weight and body weight gain. Further clinical effects of systemic toxicity were not described and no clinico-chemical investigation or pathology other than for skin lesions was performed.
Skin effects:
14%: all animals showed skin lesions ranging from erythema and crust formation to ulceration. This was affirmed pathologically and histology revealed acanthosis and fibrous condensation with inflammation of connective tissue.
10%: 6/10 animals showed skin lesions which were in general less pronounced than in the high concentration. The same histological findings as in the high concentration group occured. 8%: no clinically detectable skin lesions were seen but in 5 animals histological alterations as described above could be detected.
The results of the study indicate that a non-irritant concentration lies below 8% and the MTD between 10 and 14%.
Source: BASF AG Ludwigshafen
Test substance: Propionic acid

(67)

Species: Syrian hamster **Sex:** male/female
Strain:
Route of admin.: oral feed
Exposure period: 7 days
Frequency of treatment: continued
Post. obs. period: no
Doses: 4 % in diet
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Result: Test- and control group consisted of 5 male and 5 female rats. No significant clinical signs were recorded during the treatment.
The stomachs of the hamsters recieving propionic acid in diet were normal but one hamster had haemorrhagic lungs. In the forestomachs nuclear vacuolation and thinning of the epithelium in the limiting ridges was reported.
Source: BASF AG Ludwigshafen

(66) (64)

Species: dog **Sex:** male/female
Strain: Beagle
Route of admin.: oral feed
Exposure period: 90 days
Frequency of treatment: daily
Post. obs. period: control and high dosage for 6 weeks
Doses: 3000, 10000, 30000 ppm
Control Group: yes, concurrent no treatment
Method: OECD Guide-line 409 "Subchronic Oral Toxicity - Non-rodent: 90-day Study"
Year: 1981 **GLP:** yes
Test substance: other TS
Result: 4 animals per sex and exposure and untreated postexposure group. Substance intake about 200, 700 and 2000 mg/kg b.w.
High dosage: lack of appetite, no other substance related clinical, hematological, clinico-chemical effect. More pronounced expression of in control animals similarly occuring spontaneous epithelial hyperplasia of esophagial mucosa. This finding was reversible in the post exposure observation period. No other pathological findings.
Mid- and low-dosage groups without substance-related findings.
Source: BASF AG Ludwigshafen
Test substance: Propionic acid

(61) (68)

Species: dog **Sex:** male
Strain: Beagle
Route of admin.: oral feed
Exposure period: 90 days
Frequency of treatment: daily
Post. obs. period:
Doses: 14500,43500ppm
Control Group: yes, concurrent no treatment
Method:
Year: **GLP:** yes
Test substance: as prescribed by 1.1 - 1.4
Remark: No hematological or clinicochemical parameters determined.
Result: High dose: diarrhoea and vomiting in all animals, low dosage: only in one dog. Similar spontaneous epithelial hyperplasia of esophageal mucosa in all groups including control without relation to treatment.
Source: BASF AG Ludwigshafen

(69) (70)

Species: hen **Sex:** male
Strain:
Route of admin.: oral feed
Exposure period: 38 days
Frequency of treatment: daily
Post. obs. period:
Doses: 3%
Control Group:
Method: other: BASF-Test
Year: **GLP:** no
Test substance: other TS
Remark: The study intended to investigate the influence of propionic acid in feed on Salmonella infection. In 1 group PA was the sole aditive, in several other groups additionally Monensin and Avotan were given.
Result: No histopathological findings in crop, esophagus stomach and bowel.
Source: BASF AG Ludwigshafen
Test substance: Propionic acid

(18) (71)

Species: monkey **Sex:** no data
Strain:
Route of admin.: oral feed
Exposure period: 9 weeks
Frequency of treatment: continued
Post. obs. period: keine Angaben
Doses: 2 % Natriumpropionat in diet (= 420 mg/kg bw/day)
Control Group: no data specified
Method:
Year: **GLP:**
Test substance: other TS
Result: There were no overt toxic effects recorded in 12 monkeys that had recieved a diet containing 2 % sodium propionate for 9 weeks. Examination was limited to blood and liver.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate

(72)

Species: pig **Sex:**
Strain:
Route of admin.: oral feed
Exposure period:
Frequency of treatment:
Post. obs. period:
Doses: 3 and 4%
Control Group:
Method:
Year: **GLP:**
Test substance:
Remark: No full document available, excerpt of pathology report.
Result: 3 or 4% propionic acid in pig–feed resulted in gastritis fibrinosa and Entritis catarrhalis desquamativa of small intestine. Also fat accumulation in single liver cells or small cell clusters occured.
Source: BASF AG Ludwigshafen

(73)

Species: pig **Sex:**
Strain:
Route of admin.: oral feed
Exposure period:
Frequency of treatment:
Post. obs. period:
Doses: 1,2 and 3%
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Remark: No full document available, excerpt from part of the report.
Result: 12 animals per group. Fattening from 24 to 93kg.
No negative influence on fattening, feed utilisation and meat quality.
Source: BASF AG Ludwigshafen

(74)

5.5 Genetic Toxicity 'in Vitro'

Type: Ames test
System of testing: Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538
Concentration: no data specified
Metabolic activation: with and without
Result: negative
Method: other: according to Ames, B.N.: Mutat. Rest. 31, 347–364
Year: 1975 **GLP:** no data
Test substance: no data
Remark: Reverse mutation assay with and without metabolic activationwith S–9 mix prepared from liver homogenate of Aroclor pretreated male rats
Source: BASF AG Ludwigshafen
Test substance: calcium propionate; no data on purity of the compound

(75)

Type: Ames test
System of testing: Salmonella typhimurium TA92, TA94, TA98, TA100, TA1535, TA1537
Concentration: up to 5 mg/plate
Metabolic activation: with and without
Result: negative
Method: other: no data
Year: **GLP:** no data
Test substance: other TS
Remark: Table not readable, but result "negative" is assumed.
Source: BASF AG Ludwigshafen
Test substance: sodium propionate; no data on purity of the compound

(58) (76) (77)

Type: Ames test
System of testing: Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538
Concentration: ca. 6250, 12500, 25000 mg/l (0.625, 1.25, 2.5 % (W/V))
Metabolic activation: with and without
Result: negative
Method: other: no data
Year: **GLP:** no
Test substance: other TS
Remark: Plate test and suspension test both with and without metabolic activation with S-9 prepared from tissue homegenate of male ICR mice, male Sprague-Dawley rats, and male monkeys (macaca mulatta).
Probably, this study is identical to the studies submiited by Litton Bionetics PB266 897 (1976) and cited in Patty, Vol. IIIC (1982), pp. 4906-4979.
Source: BASF AG Ludwigshafen
Test substance: sodium propionate; no data on purity of the compound

(78)

Type: Ames test
System of testing: Salomonella typhimurium, no data on tester strain
Concentration: ca. 100, 200, 400 mg/l (100, 200, 400 ppm)
Metabolic activation: no data
Result: negative
Method: other: no data
Year: **GLP:** no data
Test substance: no data
Remark: recombination assay in presence of sodium nitrite; only abstract anvailable; no further data
Source: BASF AG Ludwigshafen
Test substance: calcium propionate; no data on purity of the compound

(79)

Type: Ames test
System of testing: S.typhimurium NTP standardbattery
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: BASF AG Ludwigshafen

(80)

Type: Ames test
System of testing: S.typhimurium TA98,100
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Sodium-propionate

(81)

Type: Ames test
System of testing: S.typhimurium TA 92,94,98,100,1535,1537
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance: other TS
Remark: -5mg/plate
Table not readable, but result "negative" is assumed.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate

(58) (82) (83)

Type: Ames test
System of testing: S.typhimurium TA 92,94,98,100,1535,1537
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance: other TS
Remark: -10mg/plate.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate

(58) (82)

Type: Ames test
System of testing: S.typhimurium TA 98,100,1535,1537,1538
Concentration: 0,095% (0,95 mg/ml)
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Remark: S9 from rat, mouse and hamster.
Plate- and suspensiontest
Source: BASF AG Ludwigshafen
(58) (19) (84)

Type: Ames test
System of testing: S.typhimurium TA98,100,1353,1357
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Remark: 0,01-10ul/plate.
Source: BASF AG Ludwigshafen
(58) (85)

Type: Ames test
System of testing: S.typhimurium TA 98, 100, 1535, 1537, 1538
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Source: BASF AG Ludwigshafen
(86)

Type: Ames test
System of testing: S.typhimurium TA98,100
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Sodium-propionate
(87) (88)

Type: Ames test
System of testing: S.typhimurium TA 92,94,98,100,1535,1537
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance: other TS
Remark: -10mg/plate.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate

(58) (76)

Type: Bacillus subtilis recombination assay
System of testing: Bacillus subtilis H17(rec+), M45(rec-)
Concentration: no data specified
Metabolic activation: without
Result: negative
Method: other: according to Shirasu, Y. et al.: Mutat. Res. 56, 121-129
Year: 1977 **GLP:** no data
Test substance: no data
Remark: paper disk method
Source: BASF AG Ludwigshafen
Test substance: calcium propionate; no data on purity of the compound

(75)

Type: Bacillus subtilis recombination assay
System of testing: Bacillus subtilis M45 rec-, H17 rec+
Concentration: ca. 100, 200, 400 mg/l (100, 200, 400 ppm)
Metabolic activation: no data
Result: negative
Method: other: no data
Year: **GLP:** no data
Test substance: no data
Remark: recombination assay in presence of sodium nitrite; only abstract anvailable; no further data
Source: BASF AG Ludwigshafen
Test substance: calcium propionate; no data on purity of the compound

(79)

Type: Cytogenetic assay
System of testing: CHL-cells
Concentration: up to 2 mg/ml
Metabolic activation: without
Result: negative
Method: other: no data
Year: **GLP:** no data
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: sodium propionate; no data on purity of the compound
(58) (76) (77)

Type: Cytogenetic assay
System of testing: CHL cells
Concentration:
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate
(81) (89)

Type: Cytogenetic assay
System of testing: CHL-cells
Concentration:
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance: other TS
Remark: -2mg/ml.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate
(58) (82) (83)

Type: Cytogenetic assay
System of testing: CHL-cells
Concentration:
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Remark: -2mg/ml.
slight increase of aberrations in highest concentration, no effect at 1mg/ml.
Source: BASF AG Ludwigshafen

(58) (82)

Type: Cytogenetic assay
System of testing: Human WI38 cells
Concentration: 0,4; 4; 40 mg/l
Metabolic activation:
Result: negative
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 – 1.4
Source: BASF AG Ludwigshafen

(90)

Type: Cytogenetic assay
System of testing: CHL cells
Concentration:
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate

(87) (88) (89)

Type: DNA damage and repair assay
System of testing: Bac.subtilis
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate

(81)

Type: DNA damage and repair assay
System of testing: E.coli WP2, WP67(uvrA-,polA-) und CM871(uvrA-,recA-,lexA-)
Concentration:
Metabolic activation: without
Result:
Method:
Year: **GLP:**
Test substance:
Remark: Dose: 1, 5 and 25ul.
Inhibition of strains WP67 and CM871 stronger than WP2.
Result is not evaluated by the author.
Source: BASF AG Ludwigshafen

(58) (85)

Type: DNA damage and repair assay
System of testing: Bac.subtilis
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate

(87) (88)

Type: Escherichia coli reverse mutation assay
System of testing: Escherichia coli WP2 hcr trp
Concentration: no data specified
Metabolic activation: with and without
Result: negative
Method: other: according to Ames, B.N.: Mutat. Rest. 31, 347-364
Year: 1975 **GLP:** no data
Test substance: no data
Remark: Reverse mutation assay with and without metabolic activationwith S-9 mix prepared from liver homogenate of Aroclor pretreated male rats
Source: BASF AG Ludwigshafen
Test substance: calcium propionate; no data on purity of the compound

(75)

Type: Escherichia coli reverse mutation assay
System of testing: Escherichia coli WP2, WP2 uvrA-
Concentration: ca. 100, 200, 400 mg/l (100, 200, 400 ppm)
Metabolic activation: no data
Result: negative
Method: other: no data
Year: **GLP:** no data
Test substance: no data
Remark: recombination assay in presence of sodium nitrite; only abstract anvailable; no further data
Source: BASF AG Ludwigshafen
Test substance: calcium propionate; no data on purity of the compound

(79)

Type: Sister chromatid exchange assay
System of testing: V79 cells
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Remark: 0,1-33mM.
Source: BASF AG Ludwigshafen
(58) (85)

Type: Sister chromatid exchange assay
System of testing: V79 cells
Concentration:
Metabolic activation: no data
Result:
Method:
Year: **GLP:**
Test substance:
Remark: Slightly elevated SCE. Negative control in comparison to Sodium butyrate. No further information.
Source: BASF AG Ludwigshafen
(91)

Type: Sister chromatid exchange assay
System of testing: human lymphocytes
Concentration:
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance:
Remark: slightly increase in SCE at 2.5 mM is described. According to the authors this weak SCE induction may be related to altered culture conditions. Some carboxylic acids were studied and the maximum response was, at most, 1.8 times (crotonic acid). For propionic acid the response was about 1.2 times. In contrast to the authors the result should be judged as negative.
Source: BASF AG Ludwigshafen
(92)

Type: Sister chromatid exchange assay
System of testing: human lymphocytes
Concentration:
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance:
Remark: A slight increase in SCE at 2.5 mM is described. According to the authors this weak SCE induction may be related to altered culture conditions. Some carboxylic acids were studied and the maximum response was, at most, 1.8 times (crotonic acid). For propionic acid the response was about 1.2 times. In contrast to the authors the result should be judged as negative.
Source: BASF AG Ludwigshafen

(92)

Type: Yeast gene mutation assay
System of testing: Saccharomyces cerevisiae D4
Concentration: ca. 12500, 25000, 50000 mg/l (1.25, 2.5, 5 % (W/V))
Metabolic activation: with and without
Result: negative
Method: other: no data
Year: **GLP:** no
Test substance: other TS
Remark: Plate test and suspension test both with and without metabolic activation with S-9 prepared from tissue homegenate of male ICR mice, male Sprague-Dawley rats, and male monkeys (macaca mulatta) for Ade+ and Try+ convertants.
Source: BASF AG Ludwigshafen
Test substance: sodium propionate; no data on purity of the compound

(78)

Type: other: DNA repair recassay
System of testing: Bac.subtilis H17(rec+), M45(rec-)
Concentration:
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Remark: paper disk method
Source: BASF AG Ludwigshafen

(86)

Type: other: E.coli reverse mutation assay
System of testing: E.coli WP2 hcr trp
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Source: BASF AG Ludwigshafen

(86)

Type: other: Gene conversion assay
System of testing: Sac. cerevisiae D4
Concentration: 2,5% 25 mg/ml
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: BASF AG Ludwigshafen

(58) (19) (84)

Type: other: Gene conversion assay
System of testing: Sac. cerevisiae D4
Concentration: 2,5% 25 mg/ml
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: BASF AG Ludwigshafen

(87) (19)

Type: other: Micronucleus Test
System of testing: Tradescantia paludosa clone 03
Concentration: 0,25-1%
Metabolic activation: without
Result: ambiguous
Method:
Year: **GLP:**
Test substance:
Remark: Increase of the number of micronuclei in highest concentration.
Source: BASF AG Ludwigshafen

(93)

Type: other: Micronucleus Test
System of testing: Tradescantia paludosa clone 03
Concentration: 0,2-1 mM
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Source: BASF AG Ludwigshafen

(93)

Type: other: Micronucleus Test
System of testing: Tradescantia paludosa clone 03
Concentration: 0,25-1%
Metabolic activation: without
Result: ambiguous
Method:
Year: **GLP:**
Test substance: other TS
Remark: Increase of the number of micronuclei in highest concentration.
Source: BASF AG Ludwigshafen
Test substance: propionic acid

(93)

Type: other: Micronucleus Test
System of testing: Tradescantia paludosa clone 03
Concentration: 0,2-1 mM
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: propionic acid, Ca

(93)

Type: other: Punktmutation
System of testing: silkworm
Concentration:
Metabolic activation:
Result: negative
Method:
Year: **GLP:**
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate

(81)

Type: other: Punktmutation
System of testing: silkworm
Concentration:
Metabolic activation:
Result: negative
Method:
Year: **GLP:**
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate
(87)

Type: other: SOS-Chromotest
System of testing: E.coli PQ37
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Remark: 0,01-10mM.
Source: BASF AG Ludwigshafen
(58) (85)

Type: other
System of testing: E.coli PQ37
Concentration: 0,3-33,3 mM
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance:
Remark: Toxicity at 10 and 33,3mM.
Source: BASF AG Ludwigshafen
(94)

Type: other
System of testing: E.coli Sd4-73
Concentration:
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance:
Remark: Reversion from streptomycin dependence to independence. Paper disk method.
Source: BASF AG Ludwigshafen
(95)

Type: other
System of testing: E. coli PQ37
Concentration:
Metabolic activation:
Result:
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Remark: Induction of SOS function by UV irradiation was not inhibited by calcium propionate up to 500ug/l.
Source: BASF AG Ludwigshafen

(96)

Type: other
System of testing: Bac.subtilis H17(rec+),M45(rec-)
Concentration:
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Remark: 50ul of 1% solution on paper disk
Source: BASF AG Ludwigshafen

(97)

Type: other
System of testing: S.typhimurium G46 and TA1530, Sacch.cerevisiae D3
Concentration:
Metabolic activation:
Result: negative
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Source: BASF AG Ludwigshafen

(90)

5.6 Genetic Toxicity 'in Vivo'

Type: Cytogenetic assay
Species: rat **Sex:**
Strain:
Route of admin.:
Exposure period:
Doses:
Result:
Method:
Year: **GLP:**
Test substance: other TS
Remark: bone marrow, no further details
Result: negativ
Sodium–propionate, bone marrow, no further details
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate

(98)

Type: Cytogenetic assay
Species: rat **Sex:**
Strain:
Route of admin.: oral unspecified
Exposure period: Single dose and five doses
Doses: 50, 500, 5000mg/kg
Result:
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 – 1.4
Result: No increase of chromosome aberrations in bone marrow cells
Source: BASF AG Ludwigshafen

(99)

Type: Cytogenetic assay
Species: rat **Sex:**
Strain:
Route of admin.:
Exposure period:
Doses:
Result:
Method:
Year: **GLP:**
Test substance: other TS
Remark: bone marrow, no further details
Result: negativ
Sodium–propionate, bone marrow, no further details
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate

(87)

Type: Dominant lethal assay
Species: rat **Sex:**
Strain:
Route of admin.: oral unspecified
Exposure period: Single dose
Doses: 50, 500, 5000mg/kg
Result:
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 – 1.4
Result: No dominant lethal mutations detected
Source: BASF AG Ludwigshafen
(99)

Type: Micronucleus assay
Species: Chinese hamster **Sex:** male/female
Strain:
Route of admin.: i.p.
Exposure period: once
Doses: 5ml 2,5% propionic acid/kg b.w. (=125mg/kg)
Result:
Method:
Year: **GLP:**
Test substance:
Result: Chinese hamster. 6 animals/sex. Sacrifice intervals 12, 24 and 48h p.inj.. Toxicity: 4/36 died.
No increase in number of micronuclei.
Source: BASF AG Ludwigshafen
(58) (85)

Type: other: Host mediated assay
Species: mouse **Sex:**
Strain:
Route of admin.: oral unspecified
Exposure period: Single dose and five doses
Doses: 50, 500, 5000mg/kg
Result:
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 – 1.4
Result: Increase in reversion frequency of S.typhimurium G–46 but not dose related. No mutations in strain TA1530 and Saccharomyces cerevisiae D3.
Source: BASF AG Ludwigshafen
(99)

5.7 Carcinogenicity

Species: rat **Sex:** male
Strain: other: Wistar (Han-BGA)
Route of admin.: oral feed
Exposure period: 10 animals/group 25 weeks; 20 animals/group until end of life
Frequency of treatment: daily
Post. obs. period: no
Doses: 0,4; 4% (4000; 40000ppm = 264; 2640mg/kg b.w.)
Result:
Control Group: yes
Method: other
Year: **GLP:** no
Test substance: other TS
Result: 25 weeks and 4%: hyperkeratotic and -plastic changes of forestomach mucosa, especially at the limiting ridge, 6/10 epidermal hyperplasia with beginning ulceration or papilloma formation, erosive lesions in the glandular stomach.
25 weeks and 0,4%: hyperkeratosis, hyperplasia of limiting ridge. Lifetime groups:
Survival: Control 125+/-30 weeks, 0,4% 122+/-29 weeks, 4% 121+/- 31 weeks.
Effects 4%: 17/20 papillomas partly with horny pearls or cysts, described as precancerous lesions in 5 animals. Strong mucosal hyperplasia of forestomach. 19/20 dysplasia of glanular stomach mucosa (13 multiple), 1/20 Cyst in the pyloroduodenal region, 1/20 adenomalike dysplasial proliferation in pyloric region, 1/20 fibroma and leiomyoma of jejunum. Effects 0,4%: hyperkeratosis and slight hyperplasia of limiting ridge, 10/20 proliferation of basal cells, 13/20 dysplasia of glandular stomach, 1/20 adenocarcinoma of pyloric region, 1/20 cyst in region of Brunners gland and adenomalike dysplasial proliferation in pyloric region. Control: 5/20 dysplasia of glandular stomach.
Source: BASF AG Ludwigshafen
Test substance: Propionsaeure und ihre Salze

(100) (58) (101)

Species: rat **Sex:** male
Strain: Fischer 344
Route of admin.: oral feed
Exposure period: 6 weeks
Frequency of treatment: continuously in the diet
Post. obs. period: none
Doses: ca. 2270 mg/kg/d (50000 ppm)
Result:
Control Group: yes, concurrent no treatment
Method: other: liver medium-term bioassay
Year: **GLP:** no data
Test substance: other TS
Result: The hepatocarcinogenic potential of 94 compounds was studiedin a liver medium-term in vivo bioassay for screening of carcinogens. Thirty-eight rats were injected intraperitoneally with 200 mg/kg diethylnitrosamin (DEN). Two weeks later, the rats were divided into 2 groups: 20 rats were fed a diet containing the test substance at a dose level of 50000 ppm for 6 weeks, 18 rats were fed a normal diet without any supplements and served as control. At week 3, all rats were two-thirds partially hepatectomized. After temination of exposure (8 weeks after the injection with DEN), all rats were sacrificed. Carcinogenic potential was scored by comparing the numbers (no./cm2) and areas (mm2/cm2) of induced glutathione-S-transferase placental form (GST-P) positive foci in the livers of treated rats with those of controls. Positive was scored for a significant increase (P<0.05) in quantitative values of GST-P positive foci; negative for no change or decrease.

A statistically significant increase in the number of foci 5.77/cm2 vs. 4.12/cm2 in control) was observed.(Compared to other cited control-values in this publication this DEN-alone control was very low - other DEN-alone values ranged from 4.12 to 10.8 foci/cm2) The areas of foci were not statistically significant increased (0.34 mm2/cm2 vs. 0.24 mm2/cm2 in controls). According to the authors, the test substance was classified as positive in this bioassay.
Source: BASF AG Ludwigshafen
Test substance: sodium propionate; no data on purity of the compound

(102) (103)

Species: rat **Sex:** male
Strain: other: Wistar (Han-BGA)
Route of admin.: oral feed
Exposure period: 10 animals/group 25 weeks; 20 animals/group until end of life
Frequency of treatment: daily
Post. obs. period: no
Doses: 0,4; 4% (4000; 40000ppm = 264; 2640mg/kg b.w.)
Result:
Control Group: yes
Method: other
Year: **GLP:** no
Test substance: other TS
Result: 25 weeks and 4%: hyperkeratotic and -plastic changes of forestomach mucosa, especially at the limiting ridge, 6/10 epidermal hyperplasia with beginning ulceration or papilloma formation, erosive lesions in the glandular stomach.
25 weeks and 0,4%: hyperkeratosis, hyperplasia of limiting ridge. Lifetime groups:
Survival: Control 125+/-30 weeks, 0,4% 122+/-29 weeks, 4% 121+/- 31 weeks.
Effects 4%: 17/20 papillomas partly with horny pearls or cysts, described as precancerous lesions in 5 animals. Strong mucosal hyperplasia of forestomach. 19/20 dysplasia of glanular stomach mucosa (13 multiple), 1/20 Cyst in the pyloroduodenal region, 1/20 adenomalike dysplasial proliferation in pyloric region, 1/20 fibroma and leiomyoma of jejunum. Effects 0,4%: hyperkeratosis and slight hyperplasia of limiting ridge, 10/20 proliferation of basal cells, 13/20 dysplasia of glandular stomach, 1/20 adenocarcinoma of pyloric region, 1/20 cyst in region of Brunners gland and adenomalike dysplasial proliferation in pyloric region. Control: 5/20 dysplasia of glandular stomach.
Source: BASF AG Ludwigshafen
Test substance: Propionsaeure

(100) (58) (101)

Species: rat **Sex:** male
Strain: Fischer 344
Route of admin.: other: keine Angabe
Exposure period: 6 Wochen
Frequency of treatment:
Post. obs. period:
Doses: keine Angabe
Result:
Control Group:
Method:
Year: **GLP:**
Test substance: other TS
Remark: The original article from Ito et al.: Carcinogenesis 9, 387-394 (1988) contains no data on sodium propionate.
Result: In this review article on a standardized protocol for a medium term bioassay model for carcinogenesis with DEN

initiation and partial hepatectomy sodium propionate occures in a list of chemicals with positive results.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate

(104)

5.8 Toxicity to Reproduction

-

5.9 Developmental Toxicity/Teratogenicity

Species: mouse **Sex:** female
Strain: CD-1
Route of admin.: gavage
Exposure period: day 6-15 of gestation
Frequency of treatment: daily
Duration of test: until day 17 of gestation
Doses: 3, 14, 65, 300 mg/kg/d
Control Group: yes, concurrent vehicle
Method: other: no data
Year: **GLP:** no
Test substance: other TS
Result: Groups of 25-30 mice were used. Negative controls were intubated with water, positive controls were administered 150 mg/kg/d of Aspirin. The animals were observed daily for appearance, behaviour, food and water consumption; body weights were recorded on days 0, 6, 11, 15, and 17 of gestation. On day 17 of pregnancy, the fetuses were excised by Cesarean section and examined grossly and microscopicallyfor abnormalities. The urogenital tract of each dam was examined for anatomical normality.
According to the authors, no clearly substance-related effects on pregnancy parameters or maternal or fetal survival were observed. The number of abnormalities found in the calcium propionate treated groups was not statistically
significantly different from negative controls.
Source: BASF AG Ludwigshafen
Test substance: calcium propionate

(105)

Species: rabbit **Sex:** female
Strain: Dutch
Route of admin.: gavage
Exposure period: day 6-18 of gestation
Frequency of treatment: daily
Duration of test: until day 29 of gestation
Doses: 4, 19, 86, 400 mg/kg/d
Control Group: yes, concurrent vehicle
Method: other: no data
Year: **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Result: Groups of 15-25 rabbits were used. Negative controls were intubated with water, positive controls were administered 150 mg/kg/d of Aspirin. The animals were observed daily for appearance, behaviour, food and water consumption; body weights were recorded on days 0, 6, 12, 18, and 29 of gestation. On day 29 of pregnancy, the fetuses were excised by Cesarean section and examined grossly and microscopically for abnormalities. The urogenital tract of each dam was examined for anatomical normality.
According to the authors, no clearly substance-related effects on pregnancy paramters or maternal or fetal survivalwere observed. The number of abnormalities found in the calcium propionate treated groups was not statistically significantly different from negative controls.
Source: BASF AG Ludwigshafen
Test substance: calcium propionate

(105)

Species: hamster **Sex:** female
Strain: other: outbred; no further data
Route of admin.: gavage
Exposure period: day 6-10 of gestation
Frequency of treatment: daily
Duration of test: until day 14 of gestation
Doses: 4, 19, 86, 400 mg/kg/d
Control Group: yes, concurrent vehicle
Method: other: no data
Year: **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Result: Groups of 22 golden hamsters were used. Negative controls were intubated with water, positive controls were administered 150 mg/kg/d of Aspirin. The animals were observed daily for appearance, behaviour, food and water consumption; body weights were recorded on days 0, 8, 10, and 14 of gestation. On day 14 of pregnancy, the fetuses were excised by Cesarean section and examined grossly and for visceral and skeletal abnormalities. The urogenital tract of each dam was examined for anatomical normality.
According to the authors, no clearly substance-related effects on pregnancy parameters or maternal or fetal survival were observed. The number of abnormalities found in the calcium propionate treated groups was not statistically significantly different from negative controls.

Source: BASF AG Ludwigshafen
Test substance: calcium propionate

(105)

Species: rat **Sex:**
Strain: Wistar
Route of admin.: oral unspecified
Exposure period: 10 days, days 6–15
Frequency of treatment: daily
Duration of test:
Doses: 3, 14, 65, 300mg/kg
Control Group: other: sham treated
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 – 1.4
Result: No maternal or fetal abnormalities detected.
Source: BASF AG Ludwigshafen

(106)

Species: rat **Sex:** female
Strain: Wistar
Route of admin.: oral unspecified
Exposure period: day 6–15 of gestation
Frequency of treatment: daily
Duration of test: until day 20 of gestation
Doses: 3, 14, 65, 300 mg/kg/d
Control Group: other
Method: other: no data
Year: **GLP:** no
Test substance: as prescribed by 1.1 – 1.4
Result: Groups of 24 rats were used. Negative controls were intubated with water, positive controls were administered 150 mg/kg/d of Aspirin. The animals were observed daily for appearance, behaviour, food and water consumption; body weights were recorded on days 0, 6, 11, 15, and 20 of gestation. On day 20 of pregnancy, the fetuses were excised by Cesarean section and examined grossly and microscopicallyfor abnormalities. The urogenital tract of each dam was examined for anatomical normality. According to the authors, no clearly substance–related effects on pregnancy parameters or maternal or fetal survival were observed. The number of abnormalities found in the calcium propionate treated groups was not statistically significantly different from negative controls.
Source: BASF AG Ludwigshafen
Test substance: calcium propionate

(105)

Species: mouse **Sex:**
Strain: CD–1
Route of admin.: oral unspecified
Exposure period: 10 days, days 6–15
Frequency of treatment: daily
Duration of test:
Doses: 3, 14, 65, 300mg/kg
Control Group: other: sham treated
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 – 1.4
Result: No maternal or fetal abnormalities detected.
Source: BASF AG Ludwigshafen

(106)

Species: rabbit **Sex:**
Strain: other: Hollaender
Route of admin.: oral unspecified
Exposure period: 13 days, days 6–18
Frequency of treatment: daily
Duration of test:
Doses: 4, 19, 86, 400mg/kg
Control Group: other: sham treated
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 – 1.4
Result: No maternal or fetal abnormalities detected.
Source: BASF AG Ludwigshafen

(106)

Species: hamster **Sex:**
Strain:
Route of admin.: oral unspecified
Exposure period: 5 days, days 6–10
Frequency of treatment: daily
Duration of test:
Doses: 4, 19, 86, 400mg/kg
Control Group: other: sham treated
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 – 1.4
Result: No maternal or fetal abnormalities detected.
Source: BASF AG Ludwigshafen

(106)

Species: **Sex:**
Strain:
Route of admin.: other: Injection
Exposure period:
Frequency of treatment:
Duration of test:
Doses: 10 mg/egg
Control Group:
Method:
Year: **GLP:**
Test substance: other TS
Result: Injection of up to 10mg/egg into air cell or yolc sac of preincubation or 96h incubated hen eggs resulted in LD50 values between 3,2 and 6,7mg/egg. There was a dose dependent increase in abnormalities after injection into the air cell but not after treatment via the yolc sac.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate

(107)

Species: other: chicken egg **Sex:**
Strain: other: no data
Route of admin.: other: injection into the yolk sac or into the air chamber
Exposure period: single dose
Frequency of treatment: single dose
Duration of test:
Doses: up to 10 mg/egg
Control Group: yes, concurrent no treatment
Method: other: according to McLaughlin, J. et al: Toxicol. Appl. Pharmacol. 5, 760–771
Year: 1964 **GLP:** no data
Test substance: other TS
Result: Injection of up to 10mg/egg into air cell or yolk sac of preincubation or 96h–incubated hen eggs resulted in LD50 values between 3,2 and 6,7 mg/egg. There was a dose–dependent increase in abnormalities after injection into the air cell but not after treatment via the yolk sac.
Source: BASF AG Ludwigshafen
Test substance: sodium propionate; no data on purity of the compound

(108)

5.10 Other Relevant Information

Type: Biochemical or cellular interactions
Result: The effect of the test substance on the induction of ornithine decarboxylase activity in phytohemagglutinin–(PHA)–stimulated lymphocytes was studied.The cells were prepared from bovine pharynenous lmymphnodes and incubated with 15 ug/ml PHA and 4 mM (ca. 380 ug/ml) for16 h. Therafter, the cells were harvested; the supernatant of the centrifugation (30000 g) was used for the enzyme activity assay. Ornithin decarboxylase activity was determined by the amount of 14Cputrescine formed from 5'–14C–ornithine during incubation for 60 minutes at 37

degree Centigrade.
According to the authors, the test substance caused 50% inhibition of the enzyme induction.
Source: BASF AG Ludwigshafen
Test substance: sodium propionate; no data on purity of the compound
(109)

Type: Cytotoxicity
Remark: erythroleucemic cells
Propionic acid induces erythroid differentiation of the cells at 1-2mM concentrations. Butyric acid is much more effective.
Source: BASF AG Ludwigshafen
(110)

Type: Cytotoxicity
Remark: colonic epithelial cells
Primary cultures of human epithelial cells from colon biopsies from patients with high risk of colon cancer were treated with psyllium fiber or short chain fatty acids. Propionic acid from 2-10mM decreased the number of viable cells to 45% and from 10-15mM increased the H3-Thymidine labeling index of the surviving cells to 120-140% of the control value.
Source: BASF AG Ludwigshafen
(111)

Type: Cytotoxicity
Remark: Lymphcytes
Mitogen induced proliferation of cultured lymphocytes is reversibly inhibited by propionic acid (1-10mM) without cytotoxicity (survival measured by trypan blue). Butyric acid is the most potent substance out of several short chain fatty acids.
Source: BASF AG Ludwigshafen
(112)

Type: Cytotoxicity
Remark: Yeast
Minimum inhibitory concentration in different yeast species (adapted to benzoic acid) at pH 3,5 was 2,5-13,5g/l. The inhibitory effect was not due to the pH.
Source: BASF AG Ludwigshafen
(113)

Type: Cytotoxicity
Remark: hum.leukemic lymphoblasts
CCRF-CEM cells.
After incubation in 5mM concentration the following ranking of cytotoxicity was established for short chain fatty acids by cell counting, H3-Thymidine incorporation and C14-release:
n-butyrate>propionate=n-valerate>i-butyrate>>acetate.
Source: BASF AG Ludwigshafen
(114)

Type: Cytotoxicity
Remark: HepG2 cells
PI50 = concentration which produces 50% reduction of protein content = 45mM
Source: BASF AG Ludwigshafen
(115)

Type: Cytotoxicity
Remark: colonic epithelial cells
Primary cultures of human epithelial cells from colon biopsies from patients with high risk of colon cancer were treated with psyllium fiber or short chain fatty acids. Propionic acid from 2-10mM decreased the number of viable cells to 45% and from 10-15mM increased the H3-Thymidine labeling index of the surviving cells to 120-140% of the control value.
Source: BASF AG Ludwigshafen
(111)

Type: Cytotoxicity
Remark: Lymphcytes
Mitogen induced proliferation of cultured lymphocytes is reversibly inhibited by propionic acid (1-10mM) without cytotoxicity (survival measured by trypan blue). Butyric acid is the most potent substance out of several short chain fatty acids.
Source: BASF AG Ludwigshafen
(112)

Type: Cytotoxicity
Remark: Yeast
Minimum inhibitory concentration in different yeast species (adapted to benzoic acid) at pH 3,5 was 2,5-13,5g/l. The inhibitory effect was not due to the pH.
Source: BASF AG Ludwigshafen
(113)

Type: Cytotoxicity
Remark: hum.leukemic lymphoblasts
CCRF-CEM cells.
After incubation in 5mM concentration the following ranking of cytotoxicity was established for short chain fatty acids by cell counting, H3-Thymidine incorporation and C14-release:
n-butyrate>propionate=n-valerate>i-butyrate>>acetate.
Source: BASF AG Ludwigshafen
(114)

Type: Cytotoxicity
Remark: HepG2 cells
PI50 = concentration which produces 50% reduction of protein content = 45mM
Source: BASF AG Ludwigshafen
(115)

Type: Metabolism
Remark: Summary of literature upto 1958.
Propionic acid is metabolized in mammals rapidly and entirely, the main pathway being from propionyl-CoA via Methylmalonyl-CoA after incorporation of CO2 to succinate, which is member of citric acid cycle. Minor pathways may be condensation of acetyl- and propionyl-CoA to form beta-Ketovalerianyl-CoA or metabolism to beta-alanine.
Source: BASF AG Ludwigshafen
(36)

Type: Metabolism
Remark: Summary of literature upto 1958.
Propionic acid is a natural intermediate in metabolism of odd- numbered fatty acids and amino acids (valine, isoleucine, threonine). 0-5% of volatile fatty acids in blood (0,18- 1,6mmol/l) are propionic acid. From in vitro studies metabolic rates up to 4,5g propionic acid/h for the liver of a 70kg man could be estimated.
Source: BASF AG Ludwigshafen
(36)

Type: Metabolism
Remark: Liver cell culture
Liver cell cultures of B12 deficient rats excert a decrease of propionate metabolism (1mM) to glucose or CO2. Addition of carnitin (10mM) increases the production of propionylcarnitin (10- ad fold) without altering the above pathway. Intraperitoneal administration of carnitin increases the urinary excretion of propionylcarnitin in Vit.B12 deficient rats.
Source: BASF AG Ludwigshafen
(116)

Type: Metabolism
Remark: rabbit
Oral administration (gavage) of 1000 or 3000mg/kg did not reduce acetonuria in alloxan diabetic rabbits but was lethal to 3/9 in the high dose. This was not the case in normal animals. 10mMol/kg (970mg/kg) produced no elevation in excretion of total short chain fatty acids but a shift towards excretion of acetic acid. In diabetic animals this treatment produced an increase in urinary excretion of ketone bodies, short chain fatty acid (acetic and butyric) and glucose. Propionic acid was not excreted.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate
(117)

Type: Metabolism
Remark: Summary of literature upto 1958.
Propionic acid is a natural intermediate in metabolism of odd- numbered fatty acids and amino acids (valine, isoleucine, threonine). 0-5% of volatile fatty acids in blood (0,18- 1,6mmol/l) are propionic acid. From in vitro studies metabolic rates up to 4,5g propionic acid/h for the liver of a 70kg man could be estimated.

Source: BASF AG Ludwigshafen
(36)

Type: Metabolism
Remark: Liver cell culture
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Source: BASF AG Ludwigshafen
(116)

Type: Metabolism
Remark: rabbit
Oral administration (gavage) of 1000 or 3000mg/kg did not reduce acetonuria in alloxan diabetic rabbits but was lethal to 3/9 in the high dose. This was not the case in normal animals. 10mMol/kg (970mg/kg) produced no elevation in excretion of total short chain fatty acids but a shift towards excretion of acetic acid. In diabetic animals this treatment produced an increase in urinary excretion of ketone bodies, short chain fatty acid (acetic and butyric) and glucose. Propionic acid was not excreted.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate
(117)

Type: Neurotoxicity
Remark: Ratte
1 ul injection of 120mM propionic acid solution into the dorsal hippocampus of anesthetized adult Spraque-Dawley rats (total amount = 8,88ug) did not induce histologically detectable neurotoxic brain lesions.
Source: BASF AG Ludwigshafen
(118)

Type: Toxicokinetics
Remark: rat
Vitamin B12 deficiency produced by soy bean diets led to an increase in urinary excretion of radioactivity from intraperitoneally injected H3-propionic acid. Parenteral supplementation of vit.B12 (3 doses of 5ug in 4weeks) turned excretion to normal.
Source: BASF AG Ludwigshafen
(62)

Type: other: Human data
Remark: case study
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate
(36) (45)

Type: other: Human data
Remark: clinical exp./ sensitization
Source: BASF AG Ludwigshafen
Test substance: sodium propionate
(119) (45)

Type: other: Human data
Remark: eye/mucosal irritation/human
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate
(45)

Type: other: Human data
Remark: skin irritation/human
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate
(45)

Type: other: Human data
Remark: skin irritation/human
Sodium propionate powder not irritating in clinical use.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate
(120)

Type: other: Human data
Remark: clinical exp./ sensitization
Source: BASF AG Ludwigshafen
Test substance: sodium propionate
(119) (45)

Type: other: Human data
Remark: eye/mucosal irritation/human
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate
(45)

Type: other: Human data
Remark: skin irritation/human
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate
(45)

Type: other: Human data
Remark: skin irritation/human
Sodium propionate powder not irritating in clinical use.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate
(120)

Type: other: Review
Remark: Zusammenfassende Darstellungen
Source: BASF AG Ludwigshafen
(121) (122) (123) (124) (125) (126) (127) (23) (120) (128) (64) (83) (129) (130) (131) (132) (133)

Type: other: review
Source: BASF AG Ludwigshafen
(103) (87) (88)

Type:
Remark: Narcotic effects; Rat
ED50 of 1,0m solution of sodium propionate 2800mg/kg i.p. with duration of narcosis 4-30min.
0,5m solution was not effective, ED50 i.v. about 1/10 of dose, s.c. weaker action, oral no narcotic effect, no influence of
Source: BASF AG Ludwigshafen
(36)

5.11 Experience with Human Exposure

Remark: Es liegen keine Untersuchungsberichte vor.
Source: BASF AG Ludwigshafen

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7.1 Risk Assessment

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